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FILING DATE.

APPLICATION NUMBER: 60/472,189

FILING DATE: May 20, 2003

RELATED PCT APPLICATION NUMBER: PCT/US03/18666

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05/20/03U.S. PTO  
60/472189**PROVISIONAL APPLICATION FOR PATENT COVER SHEET**

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

INVENTOR(S)		
Given Name (first and middle [if any]) Stephen F. John J. Jan T.	Family Name or Surname Hardy Donnelly III Zur Megede	Residence (City and either State or Foreign Country) San Francisco, California USA Moraga, California USA San Francisco, California USA
<input type="checkbox"/> Additional inventors are being named on the _____ separately numbered sheets attached hereto		
TITLE OF THE INVENTION (280 characters max)		
VECTORS FOR EXPRESSION OF HML-2 POLYPEPTIDES		
Direct all correspondence to: CORRESPONDENCE ADDRESS		
<input checked="" type="checkbox"/> Customer Number <b>27476</b>		Place Customer Number Bar Code Label here
OR Type Customer Number here		
<input checked="" type="checkbox"/> Firm or Individual Name <b>CHIRON CORPORATION</b>		
Address	Intellectual Property	
Address	P.O. Box 8097	
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ENCLOSED APPLICATION PARTS (check all that apply)		
<input checked="" type="checkbox"/> Specification Number of Pages	25	<input type="checkbox"/> CD(s), Number
<input checked="" type="checkbox"/> Drawing(s) Number of Sheets	7	<input checked="" type="checkbox"/> Other (specify) <b>1 p. Abstract; 3 pp. reference listing; 25 pp. sequence listing</b>
<input type="checkbox"/> Application Data Sheet. See 37 CFR 1.76		
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)		
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27.	FILING FEE	
<input checked="" type="checkbox"/> A check or money order is enclosed to cover the filing fees	AMOUNT (\$)	
<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number <b>03-1664</b>	<b>\$160.00</b>	
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.		
<input checked="" type="checkbox"/> No.		
<input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are: _____		

Respectfully submitted,

SIGNATURE TYPED or PRINTED NAME **Marcella Lillis**TELEPHONE **510-923-8406**Date **05/20/2003**REGISTRATION NO. **36,583**

(if appropriate)

Docket Number: **PP-19482.002****USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT**

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C.

PATENT  
Atty. Docket No. PP-19482.00205/20/03  
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Nancy L. Swanson  
Nancy L. Swanson

5/20/03  
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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: STEPHEN F. HARDY et al.  
 Provisional Serial No.: Unassigned  
 Filing Date: Even Date Herewith  
 Group Art Unit: Unassigned  
 Examiner: Unassigned  
 For: VECTORS FOR EXPRESSION OF HML-2 POLYPEPTIDES

TRANSMITTAL LETTER

Mail Stop: Provisional Patent Application  
 Commissioner for Patents  
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 Alexandria, VA 22313-1450

Sir:

Enclosed herewith are the following documents:

1. Provisional Application for Patent Cover Sheet
2. Specification (25 pages)
3. Drawings (7 sheets)
4. Abstract (1 page)
5. Paper Sequence Listing (25 pages)

PATENT  
Atty. Docket No. PP-19482.002

6. Reference Listing (3 pages)
7. Check in the amount of \$160.00 covering filing fee.
8. Return postcard.

The Assistant Commissioner is hereby authorized to charge any additional fees (or credit any overpayment) associated with this communication and which may be required under 37 CFR 1.16 and 1.17 to Deposit Account No. 03-1664. This, however, is not authorization to pay the issue fee.

Respectfully submitted,

By: Marcella Lillis  
Marcella Lillis  
Registration No. 36,583

Date: May 20, 2003







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polypeptide sequences are: SEQ ID 19 [HERV-K(C7)]; SEQ ID 20 [HERV-K10]; SEQ ID 21 ['ERVK6']; SEQ ID 73.

HML-2 env polypeptide is encoded by the fourth long ORF in a complete HML-2 genome. The translated polypeptide is proteolytically cleaved. Examples of env nucleotide sequences are:

5 SEQ ID 22 [HERV-K(108)]; SEQ ID 23 [HERV-K(C7)]; SEQ ID 24 [HERV-K(II)]; SEQ ID 25 [HERV-K10]. Examples of env polypeptide sequences are: SEQ ID 26 [HERV-K(C7)]; SEQ ID 27 [HERV-K10]; SEQ ID 28 ['ERVK6'].

HML-2 cORF polypeptide is encoded by an ORF which shares the same 5' region and start codon as env. After around 87 codons, a splicing event removes env-coding sequences and the 10 cORF-coding sequence continues in the reading frame +1 relative to that of env [19, 20]. cORF has also been called Rec [21]. Examples of cORF nucleotide sequences are: SEQ IDs 29 & 30 [HERV-K(108)]. An example of a cORF polypeptide sequence is SEQ ID 31.

The HML-2 polypeptide may alternatively be from a PCAP open-reading frame [22], such as PCAP1, PCAP2, PCAP3, PCAP4, PCAP4a or PCAP5 (SEQ IDs 32 to 37 herein). PCAP3 15 (SEQ IDs 34 & 46) and PCAP5 are preferred (SEQ ID 37).

The HML-2 polypeptide may alternatively be one of SEQ IDs 38 to 50 [22].

Sequences encoding any HML-2 polypeptide expression product may be used in accordance with the invention (e.g. sequences encoding any one of SEQ IDs 5, 6, 7, 8, 9, 13, 14, 19, 20, 21, 26, 27, 28, 31-50, 69-74, 78 or 79).

20 The invention may also utilize sequences encoding polypeptides having at least *a*% identity to such wild-type HML-2 polypeptide sequences. The value of *a* may be 65 or more (e.g. 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, 99.9). These sequences include allelic variants, SNP variants, homologs, orthologs, paralogs, mutants *etc.* of the SEQ IDs listed in the previous paragraph.

25 The invention may also utilize sequences having at least *b*% identity to wild-type HML-2 nucleotide sequences. The value of *b* may be 65 or more (e.g. 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, 99.9). These sequences include allelic variants, SNP variants, homologs, orthologs, paralogs, mutants *etc.* of SEQ IDs 1, 2, 3, 4, 10, 11, 12, 15, 16, 17, 18, 22, 23, 24, 25, 29 and 30.

30 The invention may also utilize sequences comprising a fragment of at least *c* nucleotides of such wild-type HML-2 nucleotide sequences. The value of *c* may be 7 or more (e.g. 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 60, 70, 75, 80, 90, 100, 125, 150, 175, 200, 250, 300 or more). The fragment is preferably a proteolytic cleavage product

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of a HML-2 polyprotein. The fragment preferably comprises a sequence encoding a T-cell or, preferably, a B-cell epitope from HML-2. T- and B-cell epitopes can be identified empirically (e.g. using the PEPSCAN method [23, 24] or similar methods), or they can be predicted e.g. using the Jameson-Wolf antigenic index [25], matrix-based approaches [26], TEPITOPE [27], 5 neural networks [28], OptiMer & EpiMer [29, 30], ADEPT [31], Tsites [32], hydrophilicity [33], antigenic index [34] or the methods disclosed in reference 35 etc.

The invention may also utilize sequences encoding a polypeptide which comprises a fragment of at least  $d$  amino acids of wild-type HML-2 polypeptide sequences. The value of  $d$  may be 7 or more (e.g. 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 10 40, 45, 50, 60, 70, 75, 80, 90, 100, 125, 150, 175, 200, 250, 300 or more). The fragment preferably comprises a T-cell or, preferably, a B-cell epitope from HML-2.

The invention may also utilize sequences comprising (i) a first sequence which is a wild-type HML-2 sequence or a sequence as disclosed above and (ii) a second non-HML-2 sequence. Examples of (ii) include sequences encoding: signal peptides, protease cleavage sites, 15 epitopes, leader sequences, tags, fusion partners, N-terminal methionine, arbitrary sequences etc. Sequence (ii) will generally be located at the N- and/or C-terminus of (i).

Even though a nucleotide sequence may encode a HML-2 polypeptide which is found naturally, it may differ from the corresponding natural nucleotide sequence. For example, the nucleotide sequence may include mutations e.g. to take into account codon preference in a host 20 of interest, or to add restriction sites or tag sequences.

#### ***THE SELECTABLE MARKER***

Vectors of the invention include a selectable marker.

The marker preferably functions in a microbial host (e.g. in a prokaryote, in a bacteria, in a yeast). The marker is preferably a prokaryotic selectable marker (e.g. transcribed under the 25 control of a prokaryotic promoter).

For convenience, typical markers are antibiotic resistance genes.

#### ***FURTHER FEATURES OF NUCLEIC ACID VECTORS OF THE INVENTION***

The vector of the invention is preferably an autonomously replicating episomal or extrachromosomal vector, such as a plasmid.

30 The vector of the invention preferably comprises an origin of replication. It is preferred that the origin of replication is active in prokaryotes but not in eukaryotes.

Preferred vectors thus include a prokaryotic marker for selection of the vector, a prokaryotic origin of replication, but a *eukaryotic* promoter for driving transcription of the

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HML-2 coding sequence. The vectors will therefore (a) be amplified and selected in prokaryotic hosts without HML-2 polypeptide expression, but (b) be expressed in eukaryotic hosts without being amplified. This is ideal for nucleic acid immunization vectors.

5 The vector of the invention may comprise a eukaryotic transcriptional terminator sequence downstream of the HML2-coding sequence. This can enhance transcription levels. Where the HML2-coding sequence does not have its own, the vector of the invention preferably comprises a polyadenylation sequence. A preferred polyadenylation sequence is from bovine growth hormone.

10 The vector of the invention may comprise a multiple cloning site  
In addition to sequences encoding a HML-2 polypeptide and a marker, the vector may comprise a second eukaryotic coding sequence. The vector may also comprise an IRES upstream of said second sequence in order to permit translation of a second eukaryotic polypeptide from the same transcript as the HML-2 polypeptide. Alternatively, the HML-2 polypeptide may be downstream of an IRES.

15 The vector of the invention may comprise unmethylated CpG motifs *e.g.* unmethylated DNA sequences which have in common a cytosine preceding a guanosine, flanked by two 5' purines and two 3' pyrimidines. In their unmethylated form these DNA motifs have been demonstrated to be potent stimulators of several types of immune cell.

#### PHARMACEUTICAL COMPOSITIONS

20 The invention provides a pharmaceutical composition comprising a vector of the invention. The invention also provides the vectors' use as medicaments, and their use in the manufacture of medicaments for treating prostate cancer. The invention also provides a method for treating a patient with a prostate tumor, comprising administering to them a pharmaceutical composition of the invention. The patient is generally a human, preferably a human male, and more preferably 25 an adult human male. Other diseases in which HERV-Ks have been implicated include testicular cancer [36], multiple sclerosis [37], and insulin-dependent diabetes mellitus (IDDM) [38], and the vectors may also be used against these diseases.

The invention also provides a method for raising an immune response, comprising administering an immunogenic dose of a vector of the invention to an animal (*e.g.* to a human).

30 Pharmaceutical compositions encompassed by the present invention include as active agent, the vectors of the invention in a therapeutically effective amount. An "effective amount" is an amount sufficient to effect beneficial or desired results, including clinical results. An effective amount can be administered in one or more administrations. For purposes of this invention, an effective amount is an amount that is sufficient to palliate, ameliorate, stabilize,

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reverse, slow or delay the symptoms and/or progression of prostate cancer. The effect can be detected by, for example, chemical markers or antigen levels. Therapeutic effects also include reduction in physical symptoms.

The precise effective amount for a subject will depend upon the subject's size and health, 5 the nature and extent of the condition, and the therapeutics or combination of therapeutics selected for administration. The effective amount for a given situation is determined by routine experimentation and is within the judgment of the clinician. For purposes of the present invention, an effective dose will generally be from about 0.01mg/kg to about 5 mg/kg, or about 0.01 mg/kg to about 50 mg/kg or about 0.05 mg/kg to about 10 mg/kg of the compositions of the 10 present invention in the individual to which it is administered.

The compositions can be used to treat cancer as well as metastases of primary cancer. In addition, the pharmaceutical compositions can be used in conjunction with conventional methods of cancer treatment, *e.g.* to sensitize tumors to radiation or conventional chemotherapy. The terms "treatment", "treating", "treat" and the like are used herein to generally refer to obtaining a 15 desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete stabilization or cure for a disease and/or adverse effect attributable to the disease. "Treatment" as used herein covers any treatment of a disease in a mammal, particularly a human, and includes: (a) preventing the disease or symptom from occurring in a 20 subject which may be predisposed to the disease or symptom but has not yet been diagnosed as having it; (b) inhibiting the disease symptom, *i.e.* arresting its development; or (c) relieving the disease symptom, *i.e.* causing regression of the disease or symptom.

A pharmaceutical composition can also contain a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" refers to a carrier for administration of a therapeutic 25 agent, such as antibodies or a polypeptide, genes, and other therapeutic agents. The term refers to any pharmaceutical carrier that does not itself induce the production of antibodies harmful to the individual receiving the composition, and which can be administered without undue toxicity. Suitable carriers can be large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid 30 copolymers, and inactive virus particles. Such carriers are well known to those of ordinary skill in the art. Pharmaceutically acceptable carriers in therapeutic compositions can include liquids such as water, saline, glycerol and ethanol. Auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, can also be present in such vehicles. Typically, the therapeutic compositions are prepared as injectables, either as liquid solutions or suspensions; 35 solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be

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prepared. Liposomes are included within the definition of a pharmaceutically acceptable carrier. Pharmaceutically acceptable salts can also be present in the pharmaceutical composition, e.g. mineral acid salts such as hydrochlorides, hydrobromides, phosphates, sulfates, and the like; and the salts of organic acids such as acetates, propionates, malonates, benzoates, and the like. A 5 thorough discussion of pharmaceutically acceptable excipients is available in reference 39.

The composition is preferably sterile and/or pyrogen-free. It will typically be buffered at about pH 7.

Once formulated, the compositions contemplated by the invention can be (1) administered directly to the subject; or (2) delivered *ex vivo*, to cells derived from the subject (e.g. as in *ex* 10 *vivo* gene therapy). Direct delivery of the compositions will generally be accomplished by parenteral injection, e.g. subcutaneously, intraperitoneally, intravenously or intramuscularly, intratumoral or to the interstitial space of a tissue. Other modes of administration include oral and pulmonary administration, suppositories, and transdermal applications, needles, and gene guns or hyposprays. Dosage treatment can be a single dose schedule or a multiple dose schedule.

15 Intramuscular injection is preferred.

Methods for the *ex vivo* delivery and reimplantation of transformed cells into a subject are known in the art [e.g. ref. 40]. Examples of cells useful in *ex vivo* applications include, for example, stem cells, particularly hematopoietic, lymph cells, macrophages, dendritic cells, or tumor cells. Generally, delivery of nucleic acids for both *ex vivo* and *in vitro* applications can be 20 accomplished by, for example, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the nucleic acid(s) in liposomes, and direct microinjection of the DNA into nuclei, all well known in the art.

Targeted delivery

Vectors of the invention may be delivered in a targeted way.

25 Receptor-mediated DNA delivery techniques are described in, for example, references 41 to 46. Therapeutic compositions containing a nucleic acid are administered in a range of about 100ng to about 200mg of DNA for local administration in a gene therapy protocol. Concentration ranges of about 500 ng to about 50 mg, about 1 $\mu$ g to about 2 mg, about 5 $\mu$ g to 30 about 500 $\mu$ g, and about 20 $\mu$ g to about 100 $\mu$ g of DNA can also be used during a gene therapy protocol. Factors such as method of action (e.g. for enhancing or inhibiting levels of the encoded gene product) and efficacy of transformation and expression are considerations which will affect the dosage required for ultimate efficacy. Where greater expression is desired over a larger area of tissue, larger amounts of vector or the same amounts re-administered in a successive protocol of administrations, or several administrations to different adjacent or close tissue portions of e.g.

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a tumor site, may be required to effect a positive therapeutic outcome. In all cases, routine experimentation in clinical trials will determine specific ranges for optimal therapeutic effect.

Vectors can be delivered using gene delivery vehicles. The gene delivery vehicle can be of viral or non-viral origin (see generally references 47 to 50).

5       Viral-based vectors for delivery of a desired nucleic acid and expression in a desired cell are well known in the art. Exemplary viral-based vehicles include, but are not limited to, recombinant retroviruses (e.g. references 51 to 61), alphavirus-based vectors (e.g. Sindbis virus vectors, Semliki forest virus (ATCC VR-67; ATCC VR-1247), Ross River virus (ATCC VR-373; ATCC VR-1246) and Venezuelan equine encephalitis virus (ATCC VR-923; ATCC VR-1250; ATCC VR 1249; ATCC VR-532); hybrids or chimeras of these viruses may also be used), poxvirus vectors (e.g. vaccinia, fowlpox, canarypox, modified vaccinia Ankara, etc.), adenovirus vectors, and adeno-associated virus (AAV) vectors (e.g. see refs. 62 to 67). Administration of DNA linked to killed adenovirus [68] can also be employed.

15      Non-viral delivery vehicles and methods can also be employed, including, but not limited to, polycationic condensed DNA linked or unlinked to killed adenovirus alone [e.g. 68], ligand-linked DNA [69], eukaryotic cell delivery vehicles cells [e.g. refs. 70 to 74] and nucleic charge neutralization or fusion with cell membranes. Naked DNA can also be employed. Exemplary naked DNA introduction methods are described in refs. 75 and 76. Liposomes (e.g. immunoliposomes) that can act as gene delivery vehicles are described in refs. 77 to 81.

20      Additional approaches are described in refs. 82 & 83.

Further non-viral delivery suitable for use includes mechanical delivery systems such as the approach described in ref. 83. Moreover, the coding sequence and the product of expression of such can be delivered through deposition of photopolymerized hydrogel materials or use of ionizing radiation [e.g. refs. 84 & 85]. Other conventional methods for gene delivery that can be used for delivery of the coding sequence include, for example, use of hand-held gene transfer particle gun [86] or use of ionizing radiation for activating transferred genes [84 & 87].

30      Delivery DNA using PLG {poly(lactide-co-glycolide)} microparticles is a particularly preferred method e.g. by adsorption to the microparticles, which are optionally treated to have a negatively-charged surface (e.g. treated with SDS) or a positively-charged surface (e.g. treated with a cationic detergent, such as CTAB).

#### Vaccine compositions

The pharmaceutical composition is preferably an immunogenic composition and is more preferably a vaccine composition. Such compositions can be used to raise antibodies in a mammal (e.g. a human) and/or to raise a cellular immune response (e.g. a response involving

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T-cells such as CTLs, a response involving natural killer cells, a response involving macrophages *etc.*)

5 The invention provides the use of a vector of the invention in the manufacture of medicaments for preventing prostate cancer. The invention also provides a method for protecting a patient from prostate cancer, comprising administering to them a pharmaceutical composition of the invention.

Nucleic acid immunization is well known [*e.g.* refs. 88 to 94 *etc.*]

10 The composition may additionally comprise an adjuvant. For example, the composition may comprise one or more of the following adjuvants: (1) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59™ [95; Chapter 10 in ref. 96], containing 5% Squalene, 0.5% Tween 80, and 0.5% Span 85 (optionally containing MTP-PE) formulated into submicron particles using a microfluidizer, (b) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-blocked polymer L121, and thr-MDP either microfluidized into a 15 submicron emulsion or vortexed to generate a larger particle size emulsion, and (c) Ribi™ adjuvant system (RAS), (Ribi Immunochem, Hamilton, MT) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (DetoxTM); (2) saponin adjuvants, such as QS21 or StimulonTM 20 (Cambridge Bioscience, Worcester, MA) may be used or particles generated therefrom such as ISCOMs (immunostimulating complexes), which ISCOMs may be devoid of additional detergent [97]; (3) Complete Freund's Adjuvant (CFA) and Incomplete Freund's Adjuvant (IFA); (4) cytokines, such as interleukins (*e.g.* IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12 *etc.*), interferons (*e.g.* gamma interferon), macrophage colony stimulating factor (M-CSF), tumor 25 necrosis factor (TNF), etc.; (5) monophosphoryl lipid A (MPL) or 3-O-deacylated MPL (3dMPL) [*e.g.* 98, 99]; (6) combinations of 3dMPL with, for example, QS21 and/or oil-in-water emulsions [*e.g.* 100, 101, 102]; (7) oligonucleotides comprising CpG motifs *i.e.* containing at least one CG dinucleotide, with 5-methylcytosine optionally being used in place of cytosine; (8) a polyoxyethylene ether or a polyoxyethylene ester [103]; (9) a polyoxyethylene sorbitan ester 30 surfactant in combination with an octoxynol [104] or a polyoxyethylene alkyl ether or ester surfactant in combination with at least one additional non-ionic surfactant such as an octoxynol [105]; (10) an immunostimulatory oligonucleotide (*e.g.* a CpG oligonucleotide) and a saponin [106]; (11) an immunostimulant and a particle of metal salt [107]; (12) a saponin and an oil-in-water emulsion [108]; (13) a saponin (*e.g.* QS21) + 3dMPL + IL-12 (optionally + a sterol) [109]; 35 (14) aluminium salts, preferably hydroxide or phosphate, but any other suitable salt may also be

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used (e.g. hydroxyphosphate, oxyhydroxide, orthophosphate, sulphate etc. [chapters 8 & 9 of ref. 96]). Mixtures of different aluminium salts may also be used. The salt may take any suitable form (e.g. gel, crystalline, amorphous etc.); (15) chitosan; (16) cholera toxin or *E.coli* heat labile toxin, or detoxified mutants thereof [110]; (17) microparticles (i.e. a particle of ~100nm to 5 ~150μm in diameter, more preferably ~200nm to ~30μm in diameter, and most preferably ~500nm to ~10μm in diameter) formed from materials that are biodegradable and non-toxic (e.g. a poly(a-hydroxy acid), a polyhydroxybutyric acid, a polyorthoester, a polyanhydride, a polycaprolactone etc., such as poly(lactide-co-glycolide) etc.) optionally treated to have a negatively-charged surface (e.g. with SDS) or a positively-charged surface (e.g. with a cationic 10 detergent, such as CTAB); (18) monophosphoryl lipid A mimics, such as aminoalkyl glucosaminide phosphate derivatives e.g. RC-529 [111]; (19) polyphosphazene (PCPP); (20) a bioadhesive [112] such as esterified hyaluronic acid microspheres [113] or a mucoadhesive selected from the group consisting of cross-linked derivatives of poly(acrylic acid), polyvinyl alcohol, polyvinyl pyrrolidone, polysaccharides and carboxymethylcellulose; (21) double-stranded RNA; or (22) other substances that act as immunostimulating agents to enhance the 15 efficacy of the composition. Aluminium salts and/or MF59™ are preferred.

Vaccines of the invention may be prophylactic (i.e. to prevent disease) or therapeutic (i.e. to reduce or eliminate the symptoms of a disease).

#### **SPECIFIC VECTORS OF THE INVENTION**

20 Preferred vectors of the invention comprise: (i) a eukaryotic promoter; (ii) a sequence encoding a HML-2 polypeptide downstream of and operably linked to said promoter; (iii) a prokaryotic selectable marker; (iv) a prokaryotic origin of replication; and (v) a eukaryotic transcription terminator downstream of and operably linked to said sequence encoding a HML-2 polypeptide.

25 Particularly preferred vectors are shown in figures 2 to 8 (SEQ IDs 51 to 56 & 80).

#### **VIRUS-LIKE PARTICLES**

HML-2 gag polypeptide has been found to assemble into virus-like particles (VLPs). This particulate form of the polypeptide has enhanced immunogenicity when compared to soluble polypeptide and is a preferred form of polypeptide for use in immunization and/or diagnosis.

30 Thus the invention provides a virus-like particle, comprising HML-2 gag polypeptide. The gag polypeptide may be myristoylated at its N-terminus.

The invention also provides a VLP of the invention for use as an immunogen or for use as a diagnostic antigen. The invention also provides the use of a VLP of the invention in the manufacture of a medicament for immunizing an animal.

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The invention also provides a method of raising an immune response in an animal, comprising administering to the animal a VLP of the invention. The immune response may comprise a humoral immune response and/or a cellular immune response.

For raising an immune response, the VLP may be administered with or without an adjuvant 5 as disclosed above. The immune response may treat or protect against cancer (e.g. prostate cancer).

The invention also provides a method for diagnosing cancer (e.g. prostate cancer) in a patient, comprising the step of contacting antibodies from the patient with VLPs of the invention. Similarly, the invention provides a method for diagnosing cancer (e.g. prostate cancer) in a 10 patient, comprising the step of contacting anti-VLP antibodies with a patient sample.

The invention also provides a process for preparing VLPs of the invention, comprising the step of expressing gag polypeptide in a cell, and collecting VLPs from the cell. Expression may be achieved using a vector of the invention.

The VLP of the invention may or may not include packaged nucleic acid.

15 The gag polypeptide from which the VLPs are made can be from any suitable HML-2 virus (e.g. SEQ IDs 1-9, 69 & 78).

#### DEFINITIONS

The term "comprising" means "including" as well as "consisting" e.g. a composition "comprising" X may consist exclusively of X or may include something additional e.g. X + Y.

20 The term "about" in relation to a numerical value x means, for example,  $x \pm 10\%$ .

The terms "neoplastic cells", "neoplasia", "tumor", "tumor cells", "cancer" and "cancer cells" (used interchangeably) refer to cells which exhibit relatively autonomous growth, so that they exhibit an aberrant growth phenotype characterized by a significant loss of control of cell 25 proliferation (i.e. de-regulated cell division). Neoplastic cells can be malignant or benign and include prostate cancer derived tissue.

References to a percentage sequence identity between two nucleic acid sequences mean that, when aligned, that percentage of bases are the same in comparing the two sequences. This alignment and the percent homology or sequence identity can be determined using software programs known in the art, for example those described in section 7.7.18 of reference 114. A 30 preferred alignment program is GCG Gap (Genetics Computer Group, Wisconsin, Suite Version 10.1), preferably using default parameters, which are as follows: open gap = 3; extend gap = 1.

References to a percentage sequence identity between two amino acid sequences means that, when aligned, that percentage of amino acids are the same in comparing the two sequences.

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This alignment and the percent homology or sequence identity can be determined using software programs known in the art, for example those described in section 7.7.18 of reference 114. A preferred alignment is determined by the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 2, BLOSUM matrix of 62. The Smith-Waterman homology search algorithm is taught in reference 115.

#### BRIEF DESCRIPTION OF DRAWINGS

Figure 1 shows the pCMVkm2 vector, and Figures 2 to 8 show vectors formed by inserting sequences encoding HML-2 polypeptides into this vector.

Figure 9 shows the location of coding sequences in the HML2.HOM genome, with nucleotide numbering according to ref. 5.

Figure 10 is a western blot showing gag expression in transfected 293 cells. Lanes 1 to 4 are: (1) gag opt HML-2; (2) gag opt PCAV; (3) gag wt PCAV; (4) mock.

Figure 11 also shows western blots of transfected 293 cells. In Figure 11A the staining antibody was anti-HML-2, but in Figure 11B it was anti-PCAV. In both 11A and 11B lanes 1 to 4 are: (1) mock; (2) gag opt HML-2; (3) gag opt PCAV; (4) gag wt PCAV. The upper arrow shows the position of gag; the lower arrow shows the  $\beta$ -actin control.

Figure 12 shows electron microscopy of 293 cells expressing (12A) gag opt PCAV or (12B) gag opt HML-2.

#### MODES FOR CARRYING OUT THE INVENTION

Certain aspects of the present invention are described in greater detail in the non-limiting examples that follow. The examples are put forth so as to provide those of ordinary skill in the art with a disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all and only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius, and pressure is at or near atmospheric.

#### Vectors for expressing HML-2 polypeptides

The basic pCMVkm2 vector is shown in figure 1. This vector has an immediate-early CMV enhancer/promoter and a bovine growth hormone transcription terminator, with a multiple cloning site in between. The vector also has a kanamycin resistance gene and a ColE1 origin of replication.

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Sequences coding for HML-2 polypeptides being inserted between *SaII* and *EcoRI* in the multiple cloning site:

Figure	SEQ ID	HML-2 polypeptide
2	51	cORF
3	52	PCAPS
4	53	gag
5	54	gag
6	55	Prt
7	56	Pol

Except for the vector shown in figure 4 (SEQ ID 53), the inserted sequences were  
5 manipulated for codon preference, including addition of an optimal stop codon:

cORF manipulation:

Start with SEQ ID 57 (SEQ ID 43); manipulate to SEQ ID 58 (SEQ ID 67):

```

10   ATGAACCCATCAGAGATGCAAAGAAAAGCACCTCCGGAGACGGAGACATC corFwt_hml (1)
      ATGAACCCAGCGAGATGCAGCGCAAGGCCCCCCCCGCGCCGCCACC corfopt_hml (1)
      GCAATCGAGCACCCTGACTCACAAGATGAACAAAATGGTGACGTAGAAAGA corFwt_hml (53)
      GCAACCGCGCCCCCTGACCCACAAGATGAACAAAGATGGTGACCGAGGAGA corfopt_hml (53)
      ACAGATGAAGTTGCCATCCACCAAGAAGGCAGAGCCGCCAACTGGGCACAA corFwt_hml (105)
      GCAGATGAAGCTGCCAGCACCAAGAAGGCCAGGCCACCTGGGCCAG corfopt_hml (105)
      CTAAGAAAGCTGACGCAGTTAGCTACAAAATATCTAGAGAACACAAAGGTGA corFwt_hml (157)
      CTGAAGAAAGCTGACCCAGCTGGCCACCAAGTACCTGGAGAACACCAAGGTGA corfopt_hml (157)
      CACAAACCCCAGAGAGTATGCTGCTTGAGCCTTGATGATTGTATCAATGGT corFwt_hml (209)
      CCCAGACCCCCGAGAGCATGCTGGCCGCCCTGATGATCGTGAGCATGGT corfopt_hml (209)
      GTCTGCAGGTGTACCCAACAGCTCCGAAGAGACAGCGACCATCGAGAACGGG corFwt_hml (261)
      GAGCGCCGGCGTGCCAACAGCAGCGAGGAGACCAGCCACCATCGAGAACGGC corfopt_hml (261)
      CCA---TGA                                     corFwt_hml (313)
      CCCGCTTAA                                     corfopt_hml (313)

```

PCAP5 manipulation:

30 Start with SEQ ID 59 (SEQ ID 37); manipulate to SEQ ID 60 (SEQ ID 68):

```

30   ATGAACCCATCGGAGATGCAAAGAAAAGCACCTCCGGAGACGGAGACAT pCAP5wt_hml (1)
      ATGAACCCAGCGAGATGCAGCGCAAGGCCCCCCCCGCGCCGCCACC pcap5opt_hml (1)
      CGCAATCGAGCACCCTGACTCACAAGATGAACAAAATGGTGACGTAGAA pCAP5wt_hml (52)
      CGCAACCGCGCCCCCTGACCCACAAGATGAACAAAGATGGTGACCGAG pcap5opt_hml (52)
      GAACAGATGAAGTTGCCATCCACCAAGAAGGCCAGAGCCCAACTGGGCA pCAP5wt_hml (103)
      GAGCAGATGAAGCTGCCAGCACCAAGAAGGCCAGGCCCCACCTGGGCC pcap5opt_hml (103)
      CAACTAAAGAAGCTGACGCAGTTAGCTACAAAATATCTAGAGAACACAAAG pCAP5wt_hml (154)
      CAGCTGAAGAAGCTGCCAGCTGGCCACCAAGTACCTGGAGAACACCAAG pcap5opt_hml (154)
      GTGACACAAACCCCAGAGAGTATGCTGCTTGAGCCTTGATGATTGTATCA pCAP5wt_hml (205)
      GTGACCCAGACCCCCGAGAGCATGCTGGCCGCCCTGATGATCGTGAGC pcap5opt_hml (205)
      ATGGTGGTGTACCCAACAGCTCCGAAGAGACAGCGACCATCGAGAACGGGC pCAP5wt_hml (256)

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5	ATGGTGGTGTACCCCACCGCCCCAAGCGCCAGCGCCCCAGCCGCACCGGC pcap5opt_hml (256)
	CATGATGACGATGGCGGTTTGTGAAAGAAAAGGGGAAATGTGGGAA pCAP5wt_hml (307)
	CACGACGACGACGGGGCTCGTGGAGAAGAAGCGCGCAAGTGGCGAG pcap5opt_hml (307)
	AAGCAAGAGAGATCAGATTGTACTGTGTGTAGAAAAGAAGTAGACAT pCAP5wt_hml (358)
	AAGCAGGAGCGCAGCGACTGCTACTGCGTGTGCGTGGAGCGCAGCCGCAC pcap5opt_hml (358)
10	AGGAGACTCCATTTGTTCTGTAC---TAA pCAP5wt_hml (409)
	CGCCGCCTGCACTTCGTGTACGCTTAA pcap5opt_hml (409)

### Gag manipulation:

Start with SEQ ID 61 (SEQ ID 69); manipulate to SEQ ID 62 (SEQ ID 70):

15	ATGGGGCAGAACTAAAAGTAAAATAAAAGTAAATATGCCCTTATCTCAGCT gagwt_hml (1) ATGGGCCAGACCAAGAGCAAGATCAAGAGCAAGTACGCCAGCTACCTGAGCT gagopt_hml (1)
	TTATTAAGGAGGGGGAGTAAAGTATCTACAAAAAATCT gagwt_hml (53) TCATCAAGATCTGCTGAAGCGCGCGCGTGAAGGTGAGCACCAAGAACCT gagopt_hml (53)
20	AATCAAGCTATTCAAATAATAGAACATTGCCCCATGGTTCCAGAACAA gagwt_hml (105) GATCAAGCTGTTCCAGATCATCGAGCAGTCTGCCCTGGTCCCCGAGCAG gagopt_hml (105)
	GGAACTTTAGATCTAAAAGATTGAAAAGAATTGTTAAGGAACCTAAACAAG gagwt_hml (157) GGCACCCCTGGACCTGAAGGACTGGAAGCGCATCGCAAGGAGCTGAAGCAGG gagopt_hml (157)
25	CAGGTAGGAAGGGTAATATCATCCACTTACAGTATGGAATGATTGGGCCAT gagwt_hml (209) CCGGCCGCAAGGGCAACATCATCCCCCTGACCGTGTGAAACGACTGGGCCAT gagopt_hml (209)
	TATTAAGCAGCTTAAAGAACCATTTCAAACAGAAGAAGATAGCGTTTCAGTT gagwt_hml (261) CATCAAGGCCGCCCTGGAGGCCCTCCAGACCGAGGAGGACAGCGTGAGCGTG gagopt_hml (261)
30	TCTGATGCCCTGGAAGCTGTATAATAGATTGTAATGAAAACACAAGGAAA gagwt_hml (313) AGCGACGCCCCCGGCAGCTGCATCATCGACTGCAACGAGAACACCCGCAAGA gagopt_hml (313)
35	AATCCCAGAAAGAACCGGAAGGTTACATTGCGAATATGTTAGCAGAGCCGGT gagwt_hml (365) AGAGCCAGAAGGAGACCGAGGGCCCTGCACTGCGAGTACGTGGCCGAGCCCGT gagopt_hml (365)
	AATGGCTCAGTCACCGAAAATGTTGACTATAATCAATTACAGGAGGTGATA gagwt_hml (417) GATGGCCCAGAGCACCCAGAACGTGGACTACAACCGAGCTGCAGGAGGTGATC gagopt_hml (417)
40	TATCCTGAAACGTTAAAATTAGAAGGAAAGGTCCAGAATTAGTGGGCCAT gagwt_hml (469) TACCCCGAGACCCCTGAAGCTGGAGGGCAAGGGCCCGAGCTGGTGGGCCCA gagopt_hml (469)
	CAGAGTCTAAACCACGAGGCACAAGTCCTCTCAGCAGGTCAAGGTGCCTGT gagwt_hml (521) GCGAGAGCAAGCCCCGGCACCCAGCCCCCTGCCGCCAGGTGCCGT gagopt_hml (521)
45	AACATTACAACCTAAAAGCAGGTTAAAGAAAATAAGACCCAAACGCCAGTA gagwt_hml (573) GACCCTGCAGCCCCAGAACGAGGTGAAGGAGAACAGACCCAGCCCCCGTG gagopt_hml (573)
	GCCTATCAAACTGGCTCCGGCTGAACCTCAGTATGCCACCCCCAGAAA gagwt_hml (625) GCCTACCAAGTACTGGCCCCCGCCGAGCTGCAGTACCGCCCCCCCCCGAGA gagopt_hml (625)
50	GTCAGTATGGATATCCAGGAATGCCACAGCACCACAGGGCAGGGGCCATA gagwt_hml (677) GCCAGTACGGCTACCCGGCATGCCACAGGGCCGCCAGGGCCCTA gagopt_hml (677)
	CCCTCAGCCGCCACTAGGAGACTTAATCTACGGCACCACTAGTAGACAG gagwt_hml (729) CCCCCAGCCCCCACCAGGCCCTGAACCCACCGCCCCCCCCAGCCGCCAG gagopt_hml (729)
55	GGTAGTAAATTACATGAAATTATTGATAATCAAGAAAGGAAGGAGATACTG gagwt_hml (781) GGCAGCAAGCTGCACGAGATCATCGACAAGAGCCGAAGGAGGGCGACACCG gagopt_hml (781)
	AGGCATGGCAATTCCCACTAACGTTAGAACCGATGCCACCTGGAGAACGGAC gagwt_hml (833) AGGCCTGGCAGTCCCCGTGACCCATGCCACAGGGCGAGGGCGC gagopt_hml (833)
60	CCAAGAGGGAGAGCCTCCCACAGTTGAGGCCAGATACAAGTCTTTCGATA gagwt_hml (885) CCAGGAGGGCGAGCCCCCACCCTGGAGGCCCTACAAGAGCTTCAGCATC gagopt_hml (885)
65	

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5	AAAAAGCTAAAGATATGAAAGAGGGAGTAAAACAGTATGGACCCAACTCCC AGAAGCTGAAGGACATGAAGGGGGCTGAAGCAGTACGGCCCCAACAGCC	gagwt_hml (937) gagopt_hml (937)
10	CTTATATGAGGACATTATTAGATTCATTGCTCATGGACATAGACTCATTCC CTACATCGCACCCCTGCTGGACAGCATGCCAACGGCCACCGCCTGATCCC	gagwt_hml (989) gagopt_hml (989)
15	TTATGATTGGAGATTCTGGAAAATCGTCTCTCACCCCTCAATTNTTA CTACGACTGGAGATCCTGGCAAGAGCAGGCTGAGCCCCAGCCAGTTCCTG	gagwt_hml (1041) gagopt_hml (1041)
20	CAATTAAAGACTTGGTGGATTGATGGGGTACAAGAACAGGTCCGAAGAAATA CAGTTCAAGACCTGGTGGATCGACGGCGTGCAGGAGCAGGTGCGCCGAACC	gagwt_hml (1093) gagopt_hml (1093)
25	GGGCTCCAATCCTCCAGTTAACATAGATGCAGATCAACTATTAGGAATAGG GCGCCGCCAACCCCCCGTGAACATCGACGCCGACCAGCTGCTGGGCATCGG	gagwt_hml (1145) gagopt_hml (1145)
30	TCAAAATTGGAGTACTATTAGTCAACAAGCATTAAATGCAAAATGAGGCCATT CCAGAACTGGAGCACCACAGCCAGCAGGCCCTGATGCAGAACGAGGCCATC	gagwt_hml (1197) gagopt_hml (1197)
35	GAGCAAGTTAGAGCTATCGCCTAGAGCCTGGAAAAATCCAAGGACCCAG GAGCAGGTGCGCGCATCTGCCTGCGCCTGGAGAAGATCCAGGACCCCG	gagwt_hml (1249) gagopt_hml (1249)
40	GAAGTACCTGCCCCCTATTTAATACAGTAACACAAGGTTCAAAAGAGGCCCTA GCAGCACCTGCCCCAGCTTCAACACCGTGCAGGCCAGGGCAGCAAGGAGGCCCTA	gagwt_hml (1301) gagopt_hml (1301)
45	TCCTGATTTGTGGCAAGGCTCCAAGATGTTGCTCAAAAGTCATTGCTGAT CCCCGACTTCGTGGCCCGCCTGCAGGACGTTGGCCAGAAGAGCATGCCGAC	gagwt_hml (1353) gagopt_hml (1353)
50	GAAAAAGCCCGTAAGGTATAGTGGAGTTGATGGCATATGAAAACGCCAATC GAGAAGGCCCGCAAGGTGATCGTGGAGCTGATGCCCTACGAGAACGCCAAC	gagwt_hml (1405) gagopt_hml (1405)
55	CTGAGTGTCAATCAGCCATTAAAGCATTAAAAGGAAAGGTTCCCTGCAGGATC CCGAGTGCCAGAGGCCATCAAGCCCTGAAGGGCAAGGTGCCGCCAG	gagwt_hml (1457) gagopt_hml (1457)
60	AGATGTAATCTCAGAATATGTAAGGCTGTGATGGAATCGGAGGAGCTATG CGACGTGATCAGCGAGTACGTGAAGGCTGCGACGGCATGGCGGCCATG	gagwt_hml (1509) gagopt_hml (1509)
65	CATAAAGCTATGCTTATGGCTCAAGCAATAACAGGAGTTGTTTAGGAGGAC CACAAGGCCATGCTGATGGCCAGGCCATCACCGCGTGGTGCCTGGCGGCC	gagwt_hml (1561) gagopt_hml (1561)
70	AAAGTTAGAACATTGGAAGAAAATGTTATAATTGTTGCTAAATTGGTCACCT AGGTGCGCACCTTCGCGCAAGTGCTACAACACTGCGGCCAGATCGGCCACCT	gagwt_hml (1613) gagopt_hml (1613)
75	AAAAAAAGAAATTGCCAGTCTTAAATAAAACAGAATATAACTATTCAAGCAACT GAAGAAGAAACTGCCCGTGTGAACAAGCAGAACATCACCATCCAGGCCACC	gagwt_hml (1665) gagopt_hml (1665)
80	ACAAACAGGTAGAGGCCACCTGACTTATGTCAGATGTAAGGAAAGGCCAC ACCACCGGCCGAGCCCCCGACCTGTGCCCGCTGCAAGAACGGCAAGC	gagwt_hml (1717) gagopt_hml (1717)
85	ATTGGGCTAGTCATGTCGTTCTAAATTGATAAAAATGGCAACCATTGTC ACTGGGCCAGCCAGTGCCGCAAGTGCAAGAACAGGCCAGGCCCTGAG	gagwt_hml (1769) gagopt_hml (1769)
90	GGGAAACCGAGCAAAGGGGCCAGCCTCAGGCCACAAACAAACTGGGGCATTC CGGCAACGAGCAGCGGGCCAGCCCCAGGCCAGCAGACCGGCCCTTC	gagwt_hml (1821) gagopt_hml (1821)
95	CCAATTCAAGCCATTGTTCTCAGGGTTTCAGGGACAACAACCCCCACTGT CCCATCCAGCCCTCGTGCCTCAGGGCTTCCAGGGCCAGCAGCCCCCTGA	gagwt_hml (1873) gagopt_hml (1873)
100	CCCAAGTGTTCAGGGAATAAGCCAGTTACCCACAATACAACAAATTGTCCCC GCCAGGTGTCCAGGGCATCAGCCAGCTGCCAGTACAACAACTGCC	gagwt_hml (1925) gagopt_hml (1925)
105	GCCACAAGCGGCAGTGCAGCAG---TAG CCCCCAGGCCGCCGTGCAAGCAGGCTAA	gagwt_hml (1977) gagopt_hml (1977)

### Prt manipulation:

65 Start with SEQ ID 63 (SEQ ID 71); manipulate to SEQ ID 64 (SEQ ID 72):

ATGTGGCCAACCATTGTGGGAAACGAGCAAAGGGGCCAGCTCAGGCCCA Protwt\_hml (1)  
ATGTGGGCCACCATCGTGGGCAAGCGCGCAAGGGCCCCGCCAGGCCCA protopt\_hml (1)

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5	CAACAAACTGGGGATTCCCAATTGCCATTGTTCTCAGGGTTTCAGG CCACCAACTGGGCATCCCCAACAGGCCATCTGCAGCAGCGCTTCAGCGG	Protwt_hml (53) protopt_hml (53)
	GACAAACACCCCCACTGTCCCAAGTGTTCAGGAATAAGCCAGTACCA CACCAACCCCCACCGTGCCCCAGCTGAGCGAACAGCCGTGACCACC	Protwt_hml (105) protopt_hml (105)
10	ATACAACAATTGTCCCCGCCAACAGCGCAGTGCAGCAGTAGATTATGTA ATCCAGCAGCTGAGCCCCGCCACCGCGCAGCGCCGCGTGGACCTGTGCA	Protwt_hml (157) protopt_hml (157)
	CTATACAAGCAGTCTCTCTGCTTCCAGGGGAGCCCCCACAAAAAACCCCC CCATCCAGGCCGTGAGCCTGCTGCCCGAGCCCCCAGAAGACCCCCAC	Protwt_hml (209) protopt_hml (209)
15	AGGGGTATATGGACCCCTGCCTAAAGGGACTGTAGGACTAATCTGGGACGA CGCGTGTACGGCCCCCTGCCAAGGGCACCGTGGCCTGATCTGGCCGC	Protwt_hml (261) protopt_hml (261)
	TCAAGTCTAAATCTAAAAGGAGTTCAAATTCTACTAGTGTGGTTGATTCA AGCAGCCTGAACCTGAAGGGCGTGCAGATCCACACCAGCGTGGTGACAGCG	Protwt_hml (313) protopt_hml (313)
20	ACTATAAAGCGAAAAATTCAATTGGTTATTAGCTCTCAATTCCCTGGAGTGC ACTACAAGGGCAGATCCAGCTGGTGATCAGCAGCAGCATCCCTGGAGCGC	Protwt_hml (365) protopt_hml (365)
	CAGTCCAAGAGACAGGATTGCTCAATTATTACTCCGCCATACATTAAGGGT CAGCCCCCGCAGCCATGCCAGCTGCTGCTGCCCTACATCAAGGGC	Protwt_hml (417) protopt_hml (417)
25	GGAAAATAGTGAATAAAAAGAATTAGGAGGGCTTGGAAAGCACTGATCCAACAG GGCAACAGCGAGATCAAGCGCATCGCCGGCTGGCAGCACCGACCCCCACCG	Protwt_hml (469) protopt_hml (469)
	GAAAGGCTGCATATTGGCAAGTCAGGTCTCAGAGAACAGACCTGTGTGAA GCAAGGCCGCTACTGGGCCAGCCAGGTGAGCGAGAACGCCCGTGTGCAA	Protwt_hml (521) protopt_hml (521)
30	GGCCATTATTCAAGGAAAACAGTTGAAGGGTTGGTAGACACTGGAGCAGAT GGCCATCATCCAGGGCAAGCAGTTGAGGGCTGGACACCGGGCGCAG	Protwt_hml (573) protopt_hml (573)
	GTCTCTATCATTGCTTAAATCAGTGGCAAAAAATTGGCCTAACAAAAGG GTGAGCATCATGCCCTGAACCAGTGGCCAAGAACTGGCCAAGCAGAAGG	Protwt_hml (625) protopt_hml (625)
35	CTGTTACAGGACTTGTGGCATAGGCACAGCCTCAGAAAGTGTATCAAAGTAC CCGTGACCGGCCTGGGGCATCGCACGCCAGCGAGGTGTACAGAGCAC	Protwt_hml (677) protopt_hml (677)
	GGAGATTTCACATTGCTTAGGGCCAGATAATCAAGAAAGTACTGTTCAGCCA CGAGATCCTGCACTGCCCTGGGCCAGAACCCAGGAGAGCACCGTGAGCCC	Protwt_hml (729) protopt_hml (729)
40	ATGATTACTCAATTCTCTTAATCTGTGGGTGAGATTATTACAACAAT ATGATCACCAGCATCCCCCTGAACCTGTGGGCCGAGCTGCTGCAGCAGT	Protwt_hml (781) protopt_hml (781)
	GGGGTGGGAAATCACCATGCCGCTCCATCATATAGCCCCACGAGTAAAAA GGGGCGCCGAGATCACCATGCCGCCAGCTACAGCCCCACCGCCAGAA	Protwt_hml (833) protopt_hml (833)
45	AATCATGACCAAGATGGGATATATACCAAGGAAAGGGACTAGGGAAAAATGAA GATCATGACCAAGATGGGCTACATCCCCGCAAGGGCTGGCAAGAACGAG	Protwt_hml (885) protopt_hml (885)
	GATGGCATTAAAATCCAGTTGAGGCTAAATAAATCAAGAAAGAGAAGGAA GACGGCAGTCAAGATCCCCGTGGAGGCCAAGATCAACCAGGAGCGCGAGGGCA	Protwt_hml (937) protopt_hml (937)
50	TAGGAAATCCTTGC---TAG TCGGCAACCCCTGCGCTTAA	Protwt_hml (989) protopt_hml (989)

### Pol manipulation:

60 Start with SEQ ID 65 (SEQ ID 73); manipulate to SEQ ID 66 (SEQ ID 74):

```
ATGAATAAATCAAGAAAGAGAAGGAATAGGGATCCTGCTAGGGCGGCCA polwt_hml (1)
ATGAACAAGAGCCGCAAGCGCCCAACCGCGAGAGCCTGCTGGCGCCGCCA polopt_hml (1)

CTGTAGAGCCTCTAAACCCATACCATTAACCTGGAAAACAGAAAAACCAAGT polwt_hml (53)
CCGTGGAGCCCCCAAGCCCATCCCCCTGACCTGGAAGACCGAGAACGCCCCGT polopt_hml (53)

GTGGGTAAATCAGTGGCGCTACCAAAACAAAAACTGGAGGTTACATTTA polwt_hml (105)
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GTGGGTGAACCAGTGGCCCCCTGCCAAGCAGAAGCTGGAGGCCCTGCACCTG polopt\_hml (105)  
 5 TTAGCAAATGAACAGTTAGAAAAGGGTCATATTGAGCCTCGTTCTCACCTT polwt\_hml (157)  
 CTGGCCAACGAGCAGCTGGAGAAGGGCCACATCGAGCCCAGCTCAGCCCCT polopt\_hml (157)  
 GGAATTCTCTGTGTTGTAAATTCAAAGAAATCAGGCAAATGGCGTATGTT polwt\_hml (209)  
 10 GGAACAGCCCCGTGTTCGTGAACGCCGTGATCCAGAAGAAGAGCGGCAAGTGGCGCATGCT polopt\_hml (209)  
 AACTGACTTAAGGGCTGTAAACGCCGTAACTCAACCCATGGGCCCTCTCAA polwt\_hml (261)  
 15 GACCGACCTGCGCGCCGTGAACGCCGTGATCCAGCCCCTGGGCCCTGCAG polopt\_hml (261)  
 CCCGGGTTGCCCTCTCCGGCCATGATCCAAAAGATTGGCCTTAAATTATAA polwt\_hml (313)  
 CCCGGCCTGCCAGCCCCGCATGATCCCCAAGGACTGGCCCTGATCATCA polopt\_hml (313)  
 20 TTGATCTAAAGGATTGCTTTTACCATCCCTCTGGCAGAGCAGGATGCGA polwt\_hml (365)  
 TCGACCTGAAGGACTGCTCTTCAACCATCCCCCTGGCCAGCAGGACTGCGA polopt\_hml (365)  
 AAAATTTGCCCTTACTATACCAAGCCATAAAATAAAAGAACGCCACAGG polwt\_hml (417)  
 25 GAAGTTCGCCCTCACCATCCCCGCATCAACAAACAAGGAGGCCACCCGC polopt\_hml (417)  
 TTTCAGTGGAAAGTGTACCTCAGGGATGCTTAATAGTCCAATTTGTC polwt\_hml (469)  
 TTCCAGTGGAAAGGTGCTGCCAGGGCATGCTGAACAGCCCCACCATCTGCC polopt\_hml (469)  
 AGACTTTGTAGGTGGCTCTCAACCAGTTAGAGAAAAGTTTCAAGACTG polwt\_hml (521)  
 30 AGACCTCGTGGGCCGCCCCCTGCAGCCCGTGCAGGAGAACAGTCAAG polopt\_hml (521)  
 TTATATTATTCAATTGATTGATATTATGCTGAGAAACGAAAGAT polwt\_hml (573)  
 CTACATCATCCACTGCACGACATCCTGCGCCGAGAACCAAGGAC polopt\_hml (573)  
 AAATTAATTGACTGTTACACATTCTGCAAGCAGAGGTTGCCAATGCTGGAC polwt\_hml (625)  
 35 AAGCTGATCGACTGCTACACCTTCTGCAGGCCAGGGTGCCAACGCCGGC polopt\_hml (625)  
 TGGCAATAGCATCTGATAAGATCCAACCTCTACTCCTTTCAATTAGG polwt\_hml (677)  
 TGCCCATGCCAGCGACAAGATCCAGACCAGCACCCCTTCACTACCTGGG polopt\_hml (677)  
 GATGCAGATAGAAAATAGAAAAATTAAAGCCACAAAAAAATAGAAATAAGAAA polwt\_hml (729)  
 40 CATGCAGATCGAGAACCGCAAGATCAAGCCCCAGAAGATCGAGATCCGCAAG polopt\_hml (729)  
 GACACATTAAAACACTAAATGATTTCAAAAATTACTAGGAGATATTAAATT polwt\_hml (781)  
 GACACCCCTGAAGACCCCTGAACGACTTCCAGAAGCTGCTGGCGACATCAACT polopt\_hml (781)  
 GGATTGGGCCACTCTAGGCATTCTACTTATGCCATGTCAAATTGTTCTC polwt\_hml (833)  
 45 GGATCCGCCCCCACCTGGCATCCCCACCTACGCCATGAGCAACCTGGTCAAG polopt\_hml (833)  
 TATCTTAAGAGGAGACTCAGACTAAATAGTAAAAGAATGTTAACCCAGAG polwt\_hml (885)  
 CATCCTGCGCGCGACAGCAGCTGAACAGCAAGCGATGCTGACCCCCGAG polopt\_hml (885)  
 GCAACAAAAGAAAATTAAATTAGTGGAGAAAAAAATTCACTGAGCAGCAAATAA polwt\_hml (937)  
 50 GCCACCAAGGAGATCAAGCTGGTGGAGGAGAACATCCAGAGGCCAGATCA polopt\_hml (937)  
 ATAGAATAGATCCCTAGCCCCACTCCAATTGATTTGCCACTGCACA polwt\_hml (989)  
 ACCGCATCGACCCCTGGCCCCCTGCAGCTGCTGATCTCGCCACCGCCCA polopt\_hml (989)  
 TTCTCCACAGGCATCATTAACTGATCTTGTGGAGTGGTCATTC polwt\_hml (1041)  
 55 CAGCCCCACCGGCATCATCCAGAACACCCGACCTGGTGGAGTGGAGCTTC polopt\_hml (1041)  
 CTTCCCTCACAGTACAGTTAAGACTTTACATTGACTTGGATCAAATAGCTA polwt\_hml (1093)  
 CTGCCCCACAGCACCGTGAAGACCTCACCTGTACCTGGACCAGATCGCCA polopt\_hml (1093)  
 60 CATTAAATCGGTACAGACAAGATTACGAATAATAAAATTATGTGGGAATGACCC polwt\_hml (1145)  
 CCCTGATCGGCCAGACCCGCTGCGCATCATCAAGCTGCGGCCACGCC polopt\_hml (1145)  
 AGACAAAATAGTTGCCCTTAACCAAGGAACAAGTTAGACAAGCCCTTATC polwt\_hml (1197)  
 65 CGACAAGATCGTGGTGGCCCTGACCAAGGAGCAGGTGCGCCAGGCCCTCATC polopt\_hml (1197)  
 AATTCTGGTGCATGGAAGATTGGTCTTGCTAATTGAGGAAATTATTGATA polwt\_hml (1249)  
 AACAGCGGCCCTGGAAGATCGGCCACTTCGTTGGCATCATCGACA polopt\_hml (1249)  
 ATCATTACCCAAAACAAAGATCTTCCAGTTCTAAATTGACTACTTGGAT polwt\_hml (1301)  
 70 ACCACTACCCCAAGACCAAGATCTTCCAGTTCTGAAGCTGACCACCTGGAT polopt\_hml (1301)

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5 TCTACCTAAAATTACCAGACGTGAACCTTAGAAAATGCTCTAACAGTATTT polwt\_hml (1353)  
 CCTGCCAAGATCACCCGCCGAGCCCCCTGGAGAACGCCCTGACCGTGTTC polopt\_hml (1353)  
 10 5 ACTGATGGTCCAGCAATGGAAAAGCAGCTTACACAGGACCGAAAAGAACGAG polwt\_hml (1405)  
 ACCGACGGCAGCAGCAACGGCAAGGCCCTACACCGGCCCCAAGGAGCGCG polopt\_hml (1405)  
 TAATCAAACACTCCATATCAATCGGCTCAAAGAGCAGAGTTGGTGCAGTCAT polwt\_hml (1457)  
 15 TGATCAAGACCCCTACCAGAGGCCAGCAGCAGCTGGTGGCCGTGAT polopt\_hml (1457)  
 10 TACAGTGTACAAGATTGACCAACCTATCAATATTATACAGATTCTGCA polwt\_hml (1509)  
 CACCGTGTGCAAGGACTTCGACCAGCCATCAACATCATCAGCAGCAGCGCC polopt\_hml (1509)  
 15 TATGTTAGTACAGGCTACAAGGGATGTTGAGACAGCTCTAATTAAATATAGCA polwt\_hml (1561)  
 TACGTGGTGCAGGCCACCCCGCAGCTGGAGACCGCCCTGATCAAGTACAGCA polopt\_hml (1561)  
 20 TGGATGATCAGTTAAACCCAGCTATTCAATTATTACAACAAACTGTAAGAAA polwt\_hml (1613)  
 TGGACGACCAGCTGAACCAAGCTGTTCAACCTGCTGCAGCAGACCGTGCAGCA polopt\_hml (1613)  
 25 AAGAAATTCCCATTATACACATATTGAGCACACACTAATTACCA polwt\_hml (1665)  
 GCGCAACTCCCCCTCATCACCATACCCACATCCGCGCCACACCAACCTGCC polopt\_hml (1665)  
 GGGCTTTGACTAAAGCAAATGAACAAGCTGACTTACTGGT-ATCATCTGCA polwt\_hml (1717)  
 25 GGCCCCCTGACCAAGGCCAAGCAGCAGGCCGACCTGCTGGTGAGCAGC-GCC polopt\_hml (1717)  
 CTCATAAAAGCACAAGAACTTCATGCTTGACTCATGTAATGCAGCAGGAT polwt\_hml (1768)  
 CTGATCAAGGCCAGGAGCTGCACGCCCTGACCCACGTGAACGCCGGCC polopt\_hml (1768)  
 30 TAAAAAACAAATTGATGTCACATGGAAACAGGCAAAAGATATTGACAAACA polwt\_hml (1820)  
 TGAAGAACAGTTGCACTGACCTGACCTGGAAGCAGGCCAAGGACATCGTCAGCA polopt\_hml (1820)  
 TTGCACCCAGTGTCAACTCTACACCTGCCACTCAAGAGGCCAGGAGTTAAT polwt\_hml (1872)  
 CTGCACCCAGTGCCAGGTGCTGCACCTGCCACCCAGGAGGCCGGCTGAAC polopt\_hml (1872)  
 35 CCCAGAGGCTGTGCTCTAATGCATTATGGCAAATGGATGTCACGATGTAC polwt\_hml (1924)  
 CCCCGCGGCCGTGCCCCAACGCCCTGTGGCAGATGGACGTGACCCACGTGC polopt\_hml (1924)  
 CTTCATTTGGAAGATTATCATATGTTCACGTAACAGTTGATACTTACACA polwt\_hml (1976)  
 40 CCAGCTTCGGCCGCTGAGCTACGTGACCGTGACCTACAGCCA polopt\_hml (1976)  
 TTTCATATGGCAAATTGACCAACAGGAGAAAGTACTTCCATGTTAAAAAA polwt\_hml (2028)  
 CTTCATCTGGGCCACCTGCCAGACCGCGAGAGCACGCCACGTGAAGAAG polopt\_hml (2028)  
 45 CATTATTGCTCTGTTGCTGAAATGGAGTTCCAGAAAAAAATCAAACACTG polwt\_hml (2080)  
 CACCTGCTGAGCTGCTCGCGTGTGGCGTGCACCG polopt\_hml (2080)  
 ACAATGGACCAAGGATATTGAGTAAAGCTTCAAGTCAGTG polwt\_hml (2132)  
 ACAACGGCCCCGGCTACTGCAGCAAGGCCCTCCAGAAAGTTCCTGAGCCAGTG polopt\_hml (2132)  
 50 GAAAATTTCACATACACAGGAATTCTTATAATTCCCAAGGACAGGCCATA polwt\_hml (2184)  
 GAAGATCAGCCACACCAACGGCATTCCACACAGGCCAGGCCATC polopt\_hml (2184)  
 GTGAAAGAACTAATAGAACACTCAAATTAGTAAACAAAAAGAAG polwt\_hml (2236)  
 55 GTGGAGGCCACCAACCGCACCTGAAGACCCAGCTGGTGAGCAGAAGGAGG polopt\_hml (2236)  
 GGGGAGACAGTAAGGAGTGTACCACTCCTCAGATGCAACTTAATCTAGCACT polwt\_hml (2288)  
 GCGCGCAGCAAGGAGTGCACCAACCCCCCAGATGCAGCTGAACCTGCCCT polopt\_hml (2288)  
 CTATACTTTAAATTAAACATTATAGAAAATCAGACTACTACTTGCA polwt\_hml (2340)  
 60 GTACACCTGAACTTCTGAAACATCTACCGCAACCAGACCCACCAGCGCC polopt\_hml (2340)  
 GAACAAACATCTACTGGTAAAAGAACAGCCCCACATGAAGGAAAACATAATT polwt\_hml (2392)  
 GAGCAGCACCTGACGGCAAGAAGAACAGCCCCACGAGGGCAAGCTGATCT polopt\_hml (2392)  
 65 GGTGGAAAGATAATAAAAGACATGGGAAATAGGGAGGTGATAACGTG polwt\_hml (2444)  
 GGTGGAAAGGACAACAAGAACAGACCTGGGAGATCGGCAGGTGATCACCTG polopt\_hml (2444)  
 GGGGAGAGGTTTGCTGTGTTCCACCAAGGAGAAAATCAGCTCCTGTTGG polwt\_hml (2496)  
 70 GGGCCGCGCTTCGCTCGGTGAGCCCCGGCGAGAACAGCTGCCGTGTGG polopt\_hml (2496)

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5 ATACCCACTAGACATTGAAGTTCTACAATGAACCCATCAGAGATGCAAAGA polwt\_hml (2548)  
 ATCCCCACCCGCCACCTGAAGTTCTACAACGAGCCATCCGCGACGCCAAGA polopt\_hml (2548)  
 AAAGCACCTCCGCGGAGACGGAGACATCGCAATCGAGCACCCTGACTCACA polwt\_hml (2600)  
 AGAGCACCAGCGCCGAGACCGAGACCCAGCCAGAGCAGCACCCTGGACAGCCA polopt\_hml (2600)  
 AGATGAACAAAATGGTGACGTCAGAAGAACAGATGAAGTGCCATCCACCAA polwt\_hml (2652)  
 GGACGAGCAGAACGGCGACGTCGCGCCGACCGAGGTTGGCCATCCACCAAG polopt\_hml (2652)  
 10 GAAGGCAGAGCCGCAACTTGGGACAACATAAGAAGCTGACGCAGTTAGCT polwt\_hml (2704)  
 GAGGGCCGCGCCGCAACCTGGGACCACCAAGGAGGCGACGCCGTGAGCT polopt\_hml (2704)  
 ACAAAATATCTAGAGAACACAAGGTGACACAAACCCAGAGAGTATGCTGC polwt\_hml (2756)  
 15 ACAAGATCAGCCGCGAGCACAAGGGCGACACCAACCCCCCGCAGTACGCCGC polopt\_hml (2756)  
 TTGCAGCCTTGATGATTGTATCAATGGTGGTAAGTCTCCCTATGCCTGCAGG polwt\_hml (2808)  
 CTGCAGCCTGGACGACTGCATCAACGGCGCAAGAGCCCTACGCCCTGCCGC polopt\_hml (2808)  
 20 AGCAGCTGCAGCAGCTAA polwt\_hml (2860)  
 AGCAGCTGCAGCAGCTAA polopt\_hml (2860)

Env manipulation:

Start with SEQ ID 81 (SEQ ID 83); manipulate to SEQ ID 82:

25 envwt\_HML2 ATGAACCCAAGCGAGATGCAAAGAAAAGCACCTCCGCGGAGACGGAGACATCGCAATCGA  
 envopt\_HML2 ATGAACCCCAGCGAGATGCAGCGCAAGGCCCCCCCCCCCCGCCACCGCAACCGC  
 envwt\_HML2 GCACCGTTGACTCACAAGATGAACAAAATGGTGACGTCAGAAGAACAGATGAAGTGCCA  
 envopt\_HML2 GCCCCCCCTGACCCACAAGATGAACAAGATGGTGACCGAGGAGCAGATGAAGCTGCC  
 30 envwt\_HML2 TCCACCAAGAAGGCCAGAGCCGCAACTTGGGACAACATAAGAAGCTGACGCAGTTAGCT  
 envopt\_HML2 AGCACCAAGAAGGCCAGAGCCCCACCTGGGCCCAGCTGAAGAAGCTGACCCAGCTGCC  
 envwt\_HML2 ACAAAATATCTAGAGAACACAAGGTGACACAAACCCAGAGAGTATGCTGCTTGCA  
 envopt\_HML2 ACCAAGTACCTGGAGAACACCAAGGTGACCCAGACCCCCAGAGCATGCTGCTGCCGCC  
 35 envwt\_HML2 TTGATGATTGTATCAATGGTGGTAAGTCTCCCTATGCCTGCAGGAGCAGCTGCAGCTAAC  
 envopt\_HML2 CTGATGATCGTGAGCATGGTGGTGAGCCTGCCCATGCCCGCCGGCGCCGCCGCCAAC  
 envwt\_HML2 TATACCTACTGGGCCTATGCTCTTCCGCCCTTAATTGGCAGTCACATGGATGGAT  
 envopt\_HML2 TACACCTACTGGGCCTACGTGCCCCCTCCCCCTGATCCGCGCGTGACCTGGATGGAC  
 envwt\_HML2 AATCCTACAGAAGTATATGTTAATGATACTGTTAGGGTACCTGGGCCATAGATGATCGC  
 envopt\_HML2 AACCCCCACCGAGGTGACGTGAACGACAGCGTGTGGGTGCCGCCATCGACGACCGC  
 45 envwt\_HML2 TGCCCTGCCAACACTGAGGAAGAAGGGATGATGATAAAATATTCCATTGGTATCATT  
 envopt\_HML2 TGCCCCGCCAACGCCCAGGGAGGGCATGATGATCAACATCAGCATCGCTACCACTAC  
 envwt\_HML2 CCTCCTATTGCTAGGGAGAGCACCAGGATGTTAATGCTGCAGTCCAAAATTGGTG  
 envopt\_HML2 CCCCCCATGCTGCCCTGGGCCGCCGGCTGCTGATGCCGCCGTGAGAATTGGCTG  
 50 envwt\_HML2 GTAGAAGTACCTACTGTCAGTCCCATCTGTAAGATTCACTTATCACATGGTAAGGGGGATG  
 envopt\_HML2 GTGGAGGTGCCAACGCTGAGCCCCATCTGCCCTTCACCTACCATGGTGAGGGCATG  
 envwt\_HML2 TCACTCAGGCCACGGGTAATTATTACAAGACTTTCTTATCAAAGATCATTAAATT  
 envopt\_HML2 AGCCTGCCCTGGCGCTGAACTACCTGCAGGACTTCAGCTACCAGCCAGCCTGAAGTTC  
 envwt\_HML2 AGACCTAAAGGGAAACCTTGCCTCAAGGAAATTCCAAAAGAATCAAAACAGAAGTT  
 envopt\_HML2 CGCCCCAACGGCAAGCCCTGCCCAAGGAGATCCCCAAGGAGAGCAAGAACACCGAGGTG  
 60 envwt\_HML2 TTAGTTGGGAAGAATGTGTGGCAATAGTGCCTGATATTACAAAACATGAATTGG  
 envopt\_HML2 CTGGTGTTGGAGGAGTGCCTGGCAACAGCGCCGTGATCCTGCAGAACACGAGTTGGC

	envwt_HML2	ACTATTATAGATTGGCACCTCGAGGTCAATTCTACCAATTGCTCAGGACAAACTCAG
	envopt_HML2	ACCATCATCGACTGGGCCCCCGGCCAGTTCTACCAACTGCAGCGGCCAGACCCAG
5	envwt_HML2	TCGTGTCCAAGTGCACAAGTGAGTCAGCTGTTGATAGCAGCTTAACAGAAAGTTAGAC
	envopt_HML2	AGCTGCCCCAGCGCCAGGTGAGCCCGCCGTGGACAGCGACCTGACCGAGAGCCTGGAC
10	envwt_HML2	AAACATAAGCATAAAAATTGCAGTCTTCTACCCCTGGGAATGGGGAGAAAAAGGAATC
	envopt_HML2	AAGCACAAGCACAAGAAGCTGCAGAGCTTACCCCTGGAGTGGGGAGAAGGGCATC
	envwt_HML2	TCTACCCCAAGACCAAAAATAGTAAGTCCTGTTCTGGTCTGAACATCCAGAATTATGG
	envopt_HML2	AGCACCCCCCGCCCAAGATCGTGAGCCCCGTAGCGGCCCCGAGCACCCCGAGCTGTGG
15	envwt_HML2	AGGCTTACTGTGGCTCACACCACATTAGAATTGGTCTGGAAATCAAACACTTAGAAACA
	envopt_HML2	CGCCTGACCGTGGCCAGCCACCACATCCGCATCTGGAGCGCAACCAGACCCCTGGAGACC
	envwt_HML2	AGAGATCGTAAGCCATTTATACTATTGACCTGAATTCCAGTCTAACAGTTCTTACAA
	envopt_HML2	CGCGACCGCAAGCCCTACACCATCGACCTGAACAGCAGCCTGACCGTGCCCCCTGCAG
20	envwt_HML2	AGTTGCGTAAAGCCCCCTTATATGCTAGTTGAGGAAATATAGTTATTAAACCAGACTCC
	envopt_HML2	AGCTGCGTGAAGCCCCCTACATGCTGGTGGTGGCAACATCGTGATCAAGCCGACAGC
	envwt_HML2	CAGACTATAACCTGTAAAATTGTAGATTGCTTACTTGCATTGATTCAACTTTAATTGG
	envopt_HML2	CAGACCACATCACCTGCGAGAACTGCCGCTGCTGACCTGCACAGCACCTTCACTGG
25	envwt_HML2	CAACACCGTATTCTGCTGGTGAGAGCAAGAGAGGGCGTGTGGATCCCTGTGTCCATGGAC
	envopt_HML2	CAGCACCGCATCCTGCTGGTGCGCCCGCGAGGGCGTGTGGATCCCGTGAGCATGGAC
	envwt_HML2	CGACCGTGGGAGGCCCTGCCATCCGCCATATTGACTGAACTTAAAGGTGTTTA
	envopt_HML2	CGCCCCCTGGGAGGCCAGCCCCAGCGTGCACATCCTGACCGAGGTGCTGAAGGGCGTGT
	envwt_HML2	AATAGATCCAAAAGATTCACTTTAATTGCACTGATTATGGGATTAATTGCACTGC
	envopt_HML2	AACCGCAGCAAGCGCTCATCTCACCCGTACCGCGTGTACATGGGCTGATGCCGTG
35	envwt_HML2	ACAGCTACGGCTGCTGTAGCAGGAGTTGCAATTGCACTCTCTGTTCACTCAGTAAACCTT
	envopt_HML2	ACCGCCACCGCCGCCGTGGCCGGCTGGCCCTGCACAGCAGCGTCAAGCGTGAACCTC
	envwt_HML2	GTAAATGATTGGCAAAAAAAATTCTACAAGATTGGAATTACAATCTAGTATTGATCAA
	envopt_HML2	GTGAACGACTGGCAGAACAGCACCCGCTGTGGAAACAGCCAGAGCAGCATCGACCAG
40	envwt_HML2	AAATTGGCAAATCAAATTAAATGATCTTAGACAAACTGTCATTGGATGGGAGACAGACTC
	envopt_HML2	AAGCTGGCCAACCAGATCAACGACCTGCGCCAGACCGTGATCTGGATGGCGACCCGCTG
	envwt_HML2	ATGAGCTTAGAACATCGTTCCAGTTACAATGTGACTGAAATCGTCAGATTGGTATT
	envopt_HML2	ATGAGCCTGGAGCACCGCTTCCAGCTGCAGTGCAGCTGGAACACCAGCGACTTCTGCATC
	envwt_HML2	ACACCCCCAAATTATAATGAGTCTGAGCATCACTGGGACATGGTAGACGCCATCTACAG
	envopt_HML2	ACCCCCCAGATCTACAACGAGAGCGAGCACCAGTGGTGCGCCGCCACCTCGCAG
50	envwt_HML2	GGAAGAGAAGATAATCTCACTTTAGACATTCCAATTAAAAGAACAAATTTCGAAGCA
	envopt_HML2	GGCCCGCGAGGAACACCTGACCCGTGACATCAGCAAGCTGAAGGAGCAGATCTCGAGGCC
	envwt_HML2	TCAAAAGCCCATTAAATTGGTGCCAGGAACCTGAGGCAATTGCAAGGAGTTGCTGATGGC
	envopt_HML2	AGCAAGGCCCCACCTGAACCTGGTGGCCGGCACCGAGGCCATGCCGGCGTGGCCGACGGC
55	envwt_HML2	CTCGCAAATCTAACCTGTCACTGGGTTAAGACCAATTGGAAGTACTACGATTATAAAAT
	envopt_HML2	CTGGCCAACCTGAACCCGTGACCTGGGTGAAGACCACTGGCAGCACCACCATCATCAAC
	envwt_HML2	CTCATATTAAATCCTTGTGTGCCTGTTGTGTTAGTCTGCAGGTGTACCCAACAG
	envopt_HML2	CTGATCCTGATCCTGGTGTGCCTGTTCTGCCTGCTGCTGGTGTGCCGTGCACCCAGCAG

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envwt_HML2	CTCCGAAGAGACAGCGACCATCGAGAACGGGCCATGATGACGATGGCGTTTGTCGAAA
envopt_HML2	CTGCGCCCGCACAGCGACCACCGCGAGCGCGCCATGATGACCATGGCGTGTGAGCAAG
5 envwt_HML2	AGAAAAGGGGAAATGTGGGAAAGCAAGAGAGATCAGATTGTTACTGTGTCTGAGGCTAA
envopt_HML2	CGCAAGGGCGGCAACGTGGCAAGAGCAAGCGCGACCAGATCGTGACCGTGAGCGTGGGCTAA

### ***IN VITRO EXPRESSION OF GAG SEQUENCES***

Three different gag-encoding sequences were cloned into the pCMVKm2 vector:

- 10 (1) gag opt HML-2 (SEQ ID 54, including SEQ ID 62 and encoding SEQ ID 70 – Fig. 5).
- (2) gag opt PCAV (SEQ ID 80, including SEQ ID 77 and encoding SEQ ID 79 – Fig. 8).
- (3) gag wt PCAV (SEQ ID 53, including SEQ ID 76 and encoding SEQ ID 78 – Fig. 4).

The vectors were used to transfect 293 cells in duplicate in 6-well plates, using the polyamine reagent *TransIt™ LT-1* (PanVera Corp, Madison WI) plus 2 µg DNA.

Cells were lysed after 48 hours and analyzed by western blot using pooled mouse antibody against HML2-gag as the primary antibody (1:400), and goat anti-mouse HRP as the secondary antibody (1:20000). Figure 10 shows that ‘gag opt PCAV’ (lane 2) expressed much more efficiently than ‘gag wt PCAV’ (lane 3). Lane 1 (‘gag opt HML-2’) is more strongly stained than lane 2 (‘gag opt PCAV’), but this could be due to the fact that the primary antibody was raised against the homologous HML-2 protein, rather than reflecting a difference in expression efficiency. To address this question, antibodies were also raised against the PCAV product and were used for Western blotting. Figure 11A shows results using the anti-HML2 as the primary antibody (1:500), and Figure 11B shows the results with anti-PCAV (1:500). Each antibody stains the homologous protein more strongly than the heterologous protein.

### ***NUCLEIC ACID IMMUNIZATION***

- 25 Vectors of the invention are purified from bacteria and used to immunize mice.

### ***T CELL RESPONSES TO PCAV GAG***

CB6F1 mice were intramuscularly immunized with pCMVKm2 vectors encoding PCAV gag (Figures 4 & 8) and induction of gag-specific CD4+ and CD8+ cells were measured.

- 30 Mice received four injections of 50µg plasmid at week 0, 2, 4 and 6. These plasmids included the wild type gag sequence (SEQ ID 76). Mice were then split into two separate groups for further work.

The first group of three mice received a further 50µg of plasmid at 25 weeks, but this plasmid included the optimized gag sequence (SEQ ID 77). Eleven days later spleens were harvested and pooled and a single cell suspension was prepared for culture. Spleen cells ( $1 \times 10^6$  per culture) were cultured overnight at 37°C in the absence (“unstimulated”) or presence

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(“stimulated”) of  $1 \times 10^7$  plaque-forming units (pfu) of a recombinant vaccinia which contains the PCAV gag sequence (“rVV-gag”, produced by homologous recombination of cloning vector pSC11 [116], followed by plaque purification of recombinant rVVgag). Duplicate stimulated and unstimulated cultures were prepared. The following day Brefeldin A was added to block cytokine secretion and cultures were continued for 2 hours. Cultures were then harvested and stained with fluorescently-labeled monoclonal antibodies for cell surface CD8 and intracellular gamma interferon (IFN-?). Stained samples were analyzed by flow cytometry and the fraction of CD8+ cells that stained positively for intracellular IFN-? was determined. Results were as follows:

Culture condition	Culture #1	Culture #2	Average
Unstimulated	0.10	0.14	0.12
Stimulated	1.51	1.27	1.39
Difference			1.27

10 An average of 1.27% of the pooled splenic CD8+ cells synthesized IFN-? in response to stimulation with rVV-gag. This demonstrates that the DNA immunization induced CD8+ T cells that specifically recognized and responded to PCAV gag.

15 The second group of four mice received a further 50 $\mu$ g of plasmid at 28 weeks, but this plasmid included the optimized gag sequence (SEQ ID 77). Twelve days later spleens were harvested. As a specificity control, a spleen was also obtained from a CB6F1 mouse that had been vaccinated with a pCMV-KM2 vector encoding HML2 env.

20 Single cell suspensions from individual spleens were prepared for culture. Spleen cells ( $1 \times 10^6$  per culture) were cultured overnight at 37°C in the absence of stimulation or in the presence of  $1 \times 10^7$  pfu rVV-gag. As a specificity control, additional cultures contained another recombinant vaccinia virus, rVV-HIVgp160env.SF162 (“rVV-HIVenv” – contains full-length env gene from SF162 isolate of HIV-1), which was not expected to cross-react with either gag or env from PCAV.

25 Duplicate cultures were prepared for each condition. The following day Brefeldin A was added to block cytokine secretion and anti-CD28 antibody was added to co-stimulate CD4 T cells. Cultures were continued for 2 hours and then harvested and stained with fluorescently-labeled monoclonal antibodies for cell surface CD8 and CD4 and intracellular IFN-?. Stained samples were analyzed by flow cytometry and the fractions of CD8+CD4- and CD4+8- T cells that stained positively for intracellular IFN-? were determined. Results are shown in the following table, expressed as the % of stained cells in response to stimulation by either PCAV gag or HIV env during spleen culture, after subtraction of the average value seen with cells which were not stimulated during spleen culture:

Spleen culture stimulation	Vector administered at 28 weeks				
	PCAV gag	PCAV gag	PCAV gag	PCAV gag	PCAV env
<b>CD8</b>					
PCAV gag	1.32	1.88	3.00	2.09	0.13
HIV env	0.04	0.12	-0.02	0.23	0.05
<b>CD4</b>					
PCAV gag	0.26	0.17	0.40	0.22	-0.01
HIV env	0.01	-0.02	-0.03	0.01	-0.02

For the 4 mice that had been vaccinated with a vector encoding PCAV gag, therefore, the rVV-gag vector stimulated 1.32% to 3.00% of CD8+ T cells to produce IFN-?. However, there were few CD8+ T cells (<0.23%) that responded to the irrelevant rVV-HIVgp160env vector. The CD8+ T cell response is thus specific to PCAV gag. Furthermore, the control mouse that 5 was immunized with PCAV env had very few CD8+ T cells (0.13%) which responded to the vaccinia stimulation.

Similarly, vaccination with PCAV gag, but not with PCAV env, induced CD4+ T cells specific for PCAV gag (0.17% to 0.40%).

10 DNA immunization with vectors encoding PCAV gag thus induces CD8+ and CD4+ T cells that specifically recognize and respond to the PCAV gag antigen.

#### ***VIRUS-LIKE PARTICLES***

293 cells were fixed 48 hours after transient transfection with pCMV-gag, either from HML-2 or from PCAV, and inspected by electron microscopy (Figure 12). VLPs were produced in both cases, but these were mainly intracellular for PCAV and mainly secreted for HML-2.

15 The assembly of viable VLPs from PCAV and HML-2 indicates that the gag protein has retained its essential activity even though the endogenous virus is "dormant" and might thus be expected to be subject to mutational inactivation.

20 The above description of preferred embodiments of the invention has been presented by way of illustration and example for purposes of clarity and understanding. It is not intended to be exhaustive or to limit the invention to the precise forms disclosed. It will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that many changes and modifications may be made thereto without departing from the spirit of the invention. It is intended that the scope of the invention be defined by the appended claims and their equivalents.

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PP-19482.002**SEQUENCE LISTING INDEX**

SEQ ID	DESCRIPTION
1-9	Gag sequences
10-14	Prt sequences
15-21	Pol sequences
22-28	Env sequences
29-31	cORF sequences
32-37	PCAP sequences
38-50	Splice variants A-M sequences
51	pCMVKm2.cORFopt HML-2 (Figure 2)
52	pCMVKm2.pCAP5opt HML-2 (Figure 3)
53	pCMVKm2.gag wt PCAV (Figure 4)
54	pCMVKm2.gagopt HML-2 (Figure 5)
55	pCMVKm2.Protopt HML-2 (Figure 6)
56	pCMVKm2.Polopt HML-2 (Figure 7)
57-66	Nucleotide sequences pre- and post-manipulation
67	Manipulated cORF
68	Manipulated PCAP5
69 & 70	Gag — pre- and post-manipulation
71 & 72	Prt — pre- and post-manipulation
73 & 74	Pol — pre- and post-manipulation
75	PCAV, from the beginning of its first 5' LTR to the end of its fragmented 3' LTR
76 & 77	PCAV Gag nucleotide sequences — pre-and post manipulation
78 & 79	PCAV Gag amino acid sequences — pre-and post manipulation
80	pCMVKm2.gagopt PCAV (Figure 8)
81	Wild-type env from HML-2
82	Optimized env from HML-2
83	Amino acid sequence encoded by SEQ IDs 81 & 82

## NB:

5     - SEQ IDs 1 to 9 disclosed in reference 1 as SEQ IDs 85, 91, 97, 102, 92, 98, 103, 104 & 146  
   - SEQ IDs 10 to 14 disclosed in reference 1 as SEQ IDs 86, 99, 105, 106 & 147  
   - SEQ IDs 15 to 21 disclosed in reference 1 as SEQ IDs 87, 93, 100, 107, 94, 108 & 148  
   - SEQ IDs 22 to 28 disclosed in reference 1 as SEQ IDs 88, 95, 101, 107, 96, 108 & 149  
   - SEQ IDs 29 to 31 disclosed in reference 1 as SEQ IDs 89, 90 & 109  
   - SEQ IDs 32 to 37 disclosed in reference 1 as SEQ IDs 10, 11, 12, 7, 8 & 9  
 10    - SEQ IDs 38 to 50 disclosed in reference 1 as SEQ IDs 28-37, 39, 41 & 43  
   - SEQ ID 75 disclosed in reference 3 as SEQ ID 1.

ABSTRACT

A nucleic acid vector comprising: (i) a promoter; (ii) a sequence encoding a HML-2 polypeptide operably linked to said promoter; and (iii) a selectable marker. Preferred vectors 5 comprise: (i) a eukaryotic promoter; (ii) a sequence encoding a HML-2 polypeptide downstream of and operably linked to said promoter; (iii) a prokaryotic selectable marker; (iv) a prokaryotic origin of replication; and (v) a eukaryotic transcription terminator downstream of and operably linked to said sequence encoding a HML-2 polypeptide. Vectors of the invention are particularly 10 useful for expression of HML-2 polypeptides either *in vitro* (e.g. for later purification) or *in vivo* (e.g. for nucleic acid immunization). They are well suited to nucleic acid immunization against prostate tumors. A preferred HML-2 is PCAV, which is located in chromosome 22 at 20.428 megabases (22q11.2).

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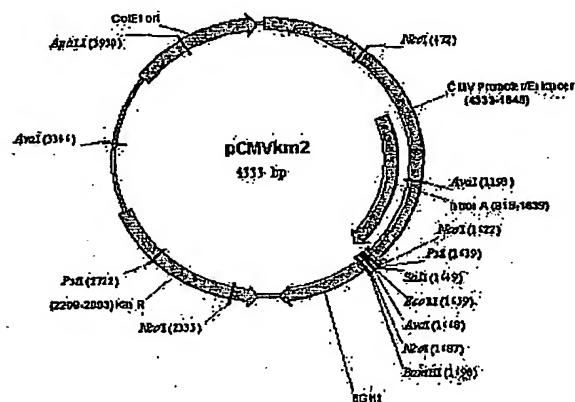
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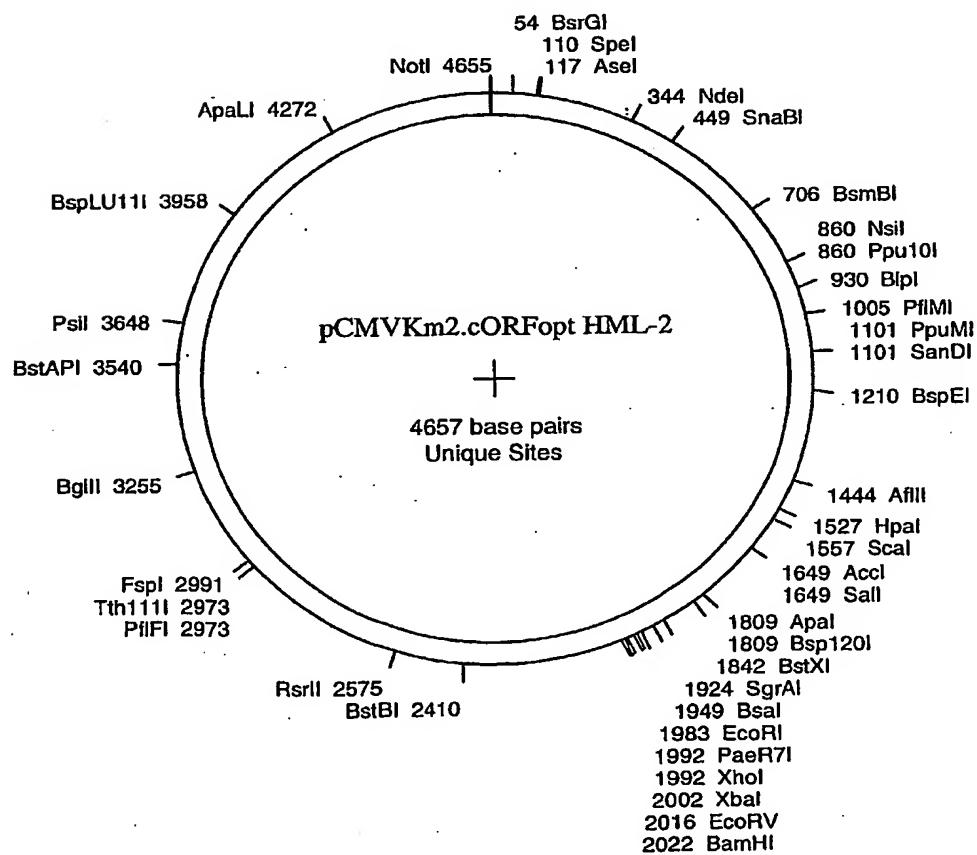
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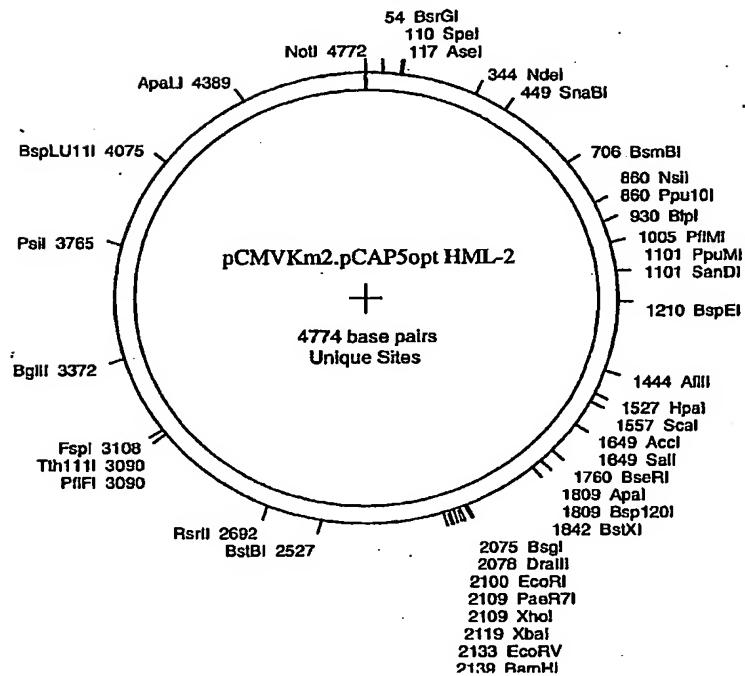
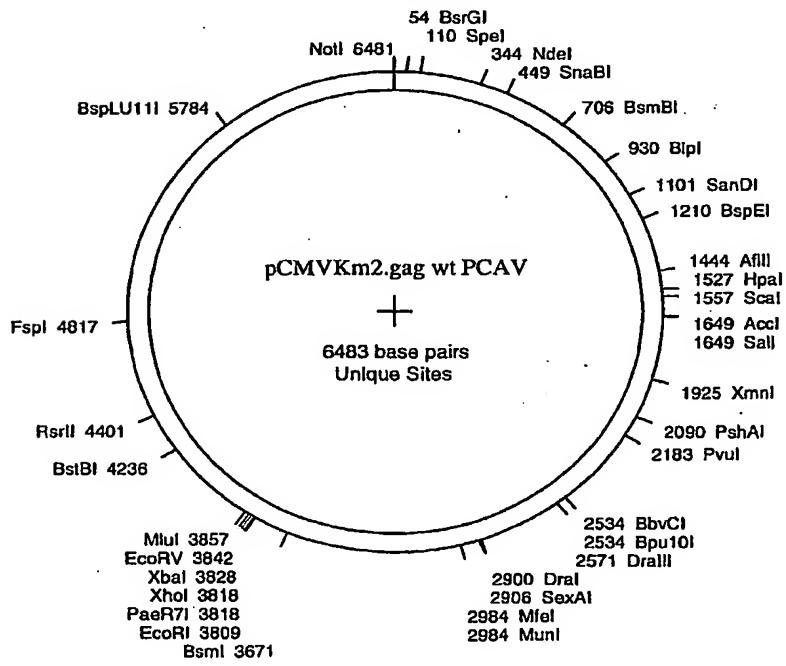
**FIGURE 1**



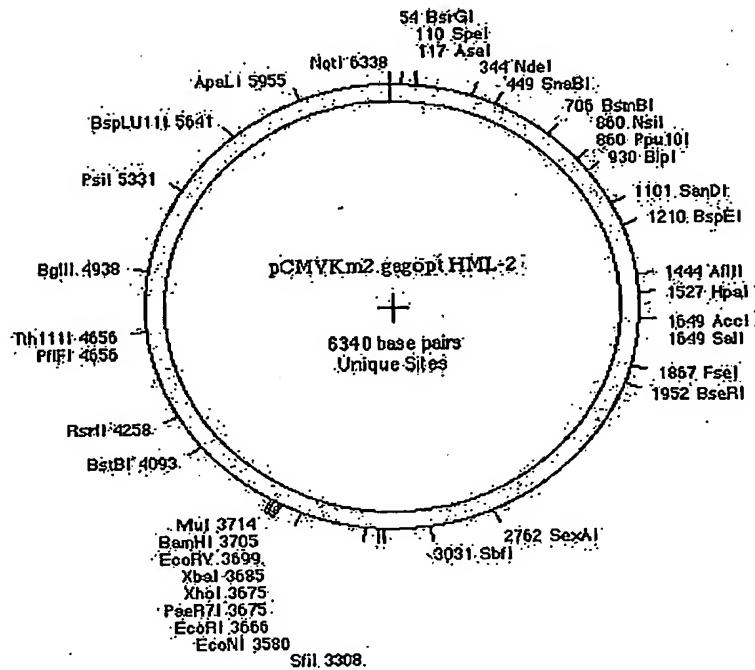
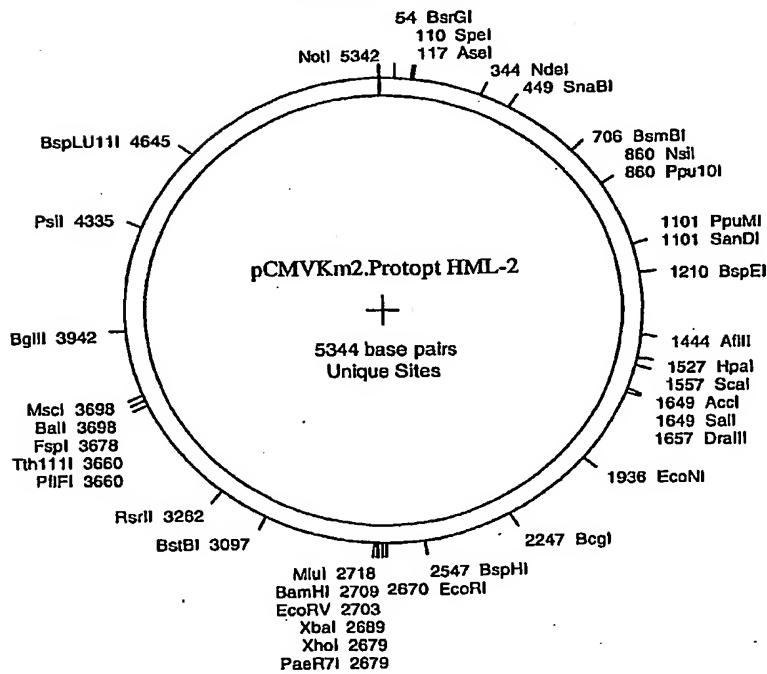
**FIGURE 2**



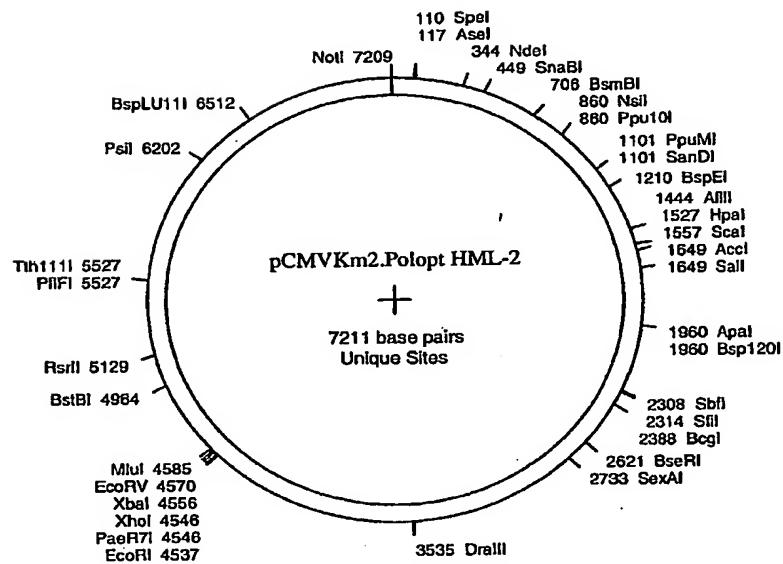
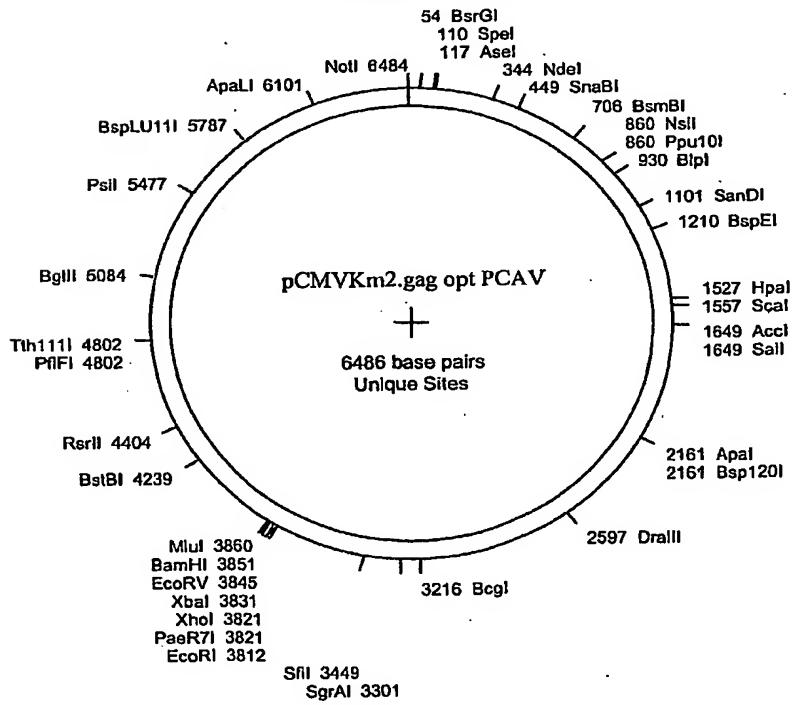
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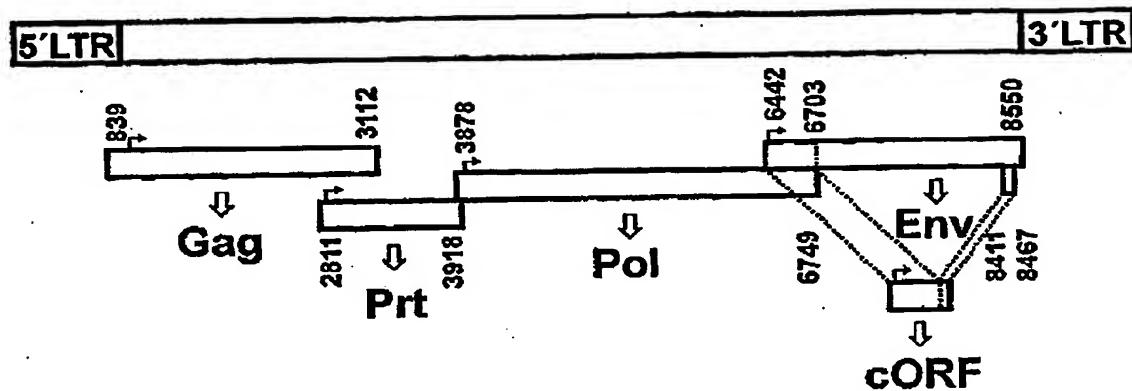
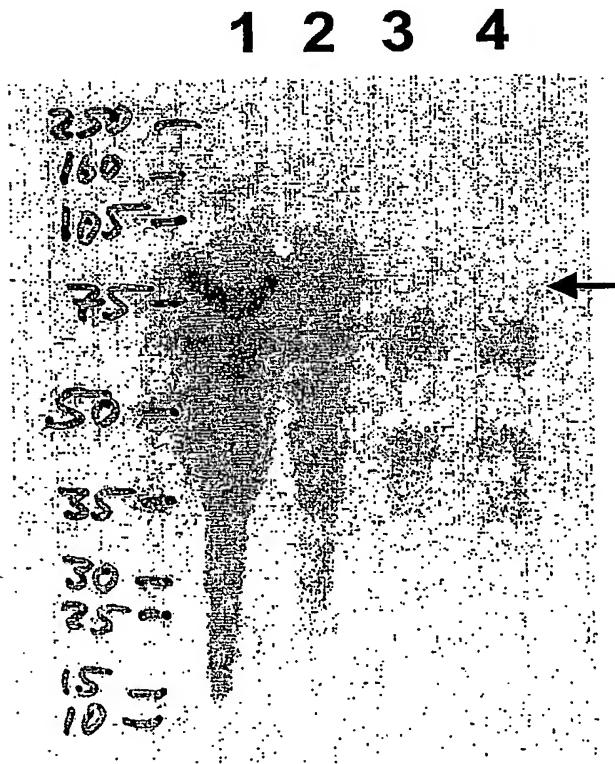
**FIGURE 3****FIGURE 4**

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**FIGURE 5****FIGURE 6**

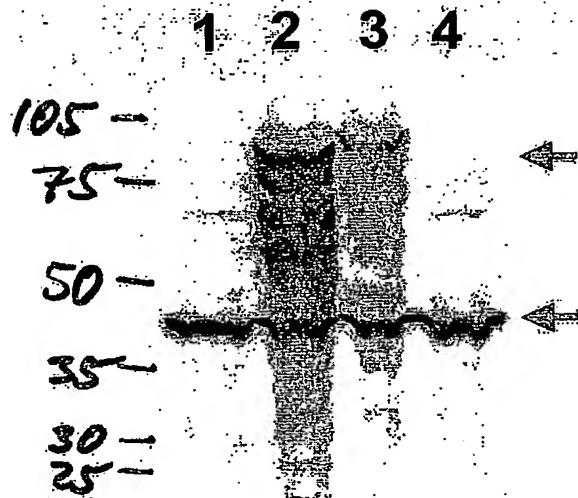
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**FIGURE 7****FIGURE 8**

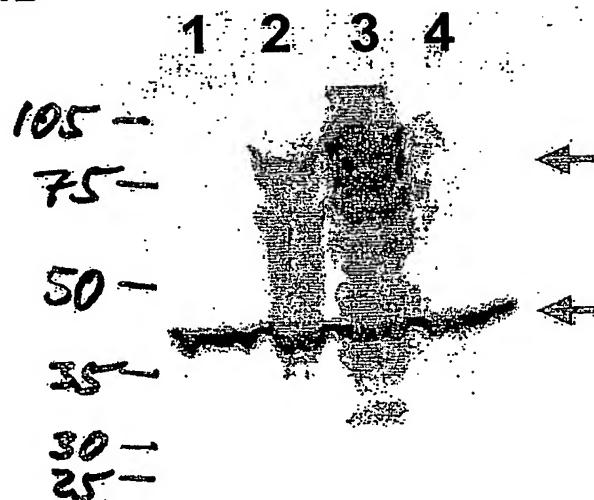
**FIGURE 9****FIGURE 10**

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**FIGURE 11A**



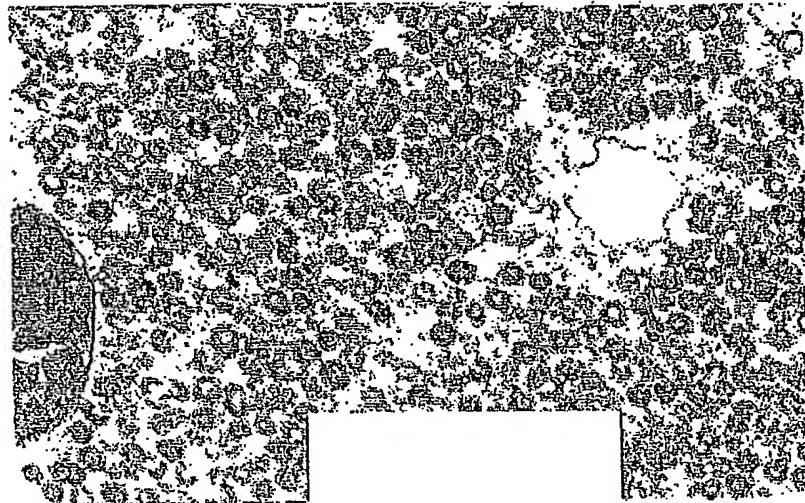
**FIGURE 11B**



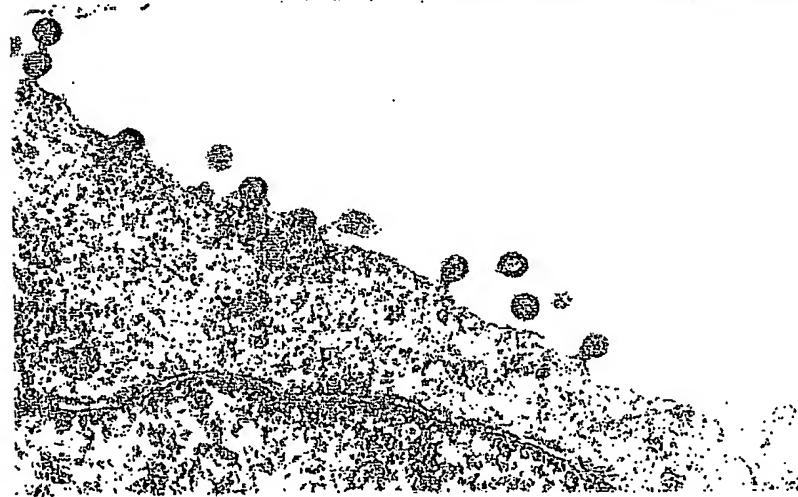
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**FIGURE 12A**



**FIGURE 12B**



## SEQUENCE LISTING

## SEQ ID 1

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CAGGGTAGTGAATTACATGAAATTATTGATAAAATCAAGAAAGGAGAGACTTGAGGCATGCAATTCCAGTAA

**SEQ ID 5**

MGQTTSKIKSKYASYLSFIKILLKRGGVVSTKNLKLQIIEQFCPWPEQGTLDLKDWRKIGKELQAGRGNIIPLTVNDWAIKAALEPFQTEEDSVSVDAPGSCIIDCNENTRKSQKETEGLHCEYVAEPVMAQSTQNVDYNQLEQVYIPETLKLEGKGPVSEKPRGTSPLPAGQVPTLQPKQVKENKTQPPVAYQWPPAELQYRPPPESQYGPMPAPQGRAPYQPPTRRLNPTAPPSRQGSKLHEIIDKSRKGDTAEWQFPVTLQPMPPGEGAQEPPPTVEARYKSFSIKKLKDMKEGVKQYGPNSPYMRTLLDSIAHGHLIIPYDWEILAKSSLSPSQFLQFKTWIDGVQEVRNRRAANPPVNIDADQLLGIGQNWSТИSQOALMNEAIEQVRAICLRAWEKIQDPGSTCPSPNTVRQGSKEPYPDFVARLQDVAQKSIADEKARKVIVELMAYENANPECQSAIKPLKGKVPAGSDVISEYVKACDGIGGAMHKAMLMAQAITGVVLGGQVRTFGKCYNCQIGHLKKNCVPVNLNKQNIITIQAATTGREPPDLCPRCKGKHWASQCRSKFDKNGQPLSGNEQRGQPQAPQQTGAFPIQPFVQPGFQGQQPLSQVFGQISQLPQYNNCPPPQAAVQQ

**SEQ ID 6**

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**SEQ ID 9**

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**SEQ ID 10**

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GAGTCAAAAATCATGACCAAGATGGATATACAGGAAAGGGACTAGGGAAAATGAAGATGGCATTAAATTCCAGTTGAGGCTAAATAAT  
CAAGAAAGAGAAGGAATAGGGATCCTTG

**SEQ ID 11**

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**SEQ ID 12**

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ACTAGGGAAAATGAAGATGGCATTAAAGTCCAGGCTAAAATAATCAAGAAAGAGAAGGAATAGGGTATCCTTTAG

**SEQ ID 13**

MEILHCLGPDNQESTVQPMITSIPLNLWGRDLLQQWGAETMPAPLSPSTSQKIMTKGYIPGKGLKNEDGIKVPVEAKINQEREGIGYPF

**SEQ ID 14**

WATIVGKRAKGPGASGPTTNWGPNSAICSSGFSGTTPTVPSVSGNPKVTTIQLSPATSGSAAVDLCTIQA VSLLPGEPPQKPTGTVYGPLPKTV  
GLILGRSSNLKGVQIHTSVVDSDYKGIEQLVIISSIPWSASPRDRIAQQLLLPYIKGGNSEIKRIGGLSTDPTGKAAYWASQVSENPVCKAIQ  
GKQFEGLVDTGADVSIALNQWPKNWPQKAVTGLVIGTASEVYQSTEILHCLGPDNQESTVQPMITSIPLNLWGRDLLQQWGAETMPAPSYSP  
SQKIMTKGYIPGKGLKNEDGIKIPVVEAKINQEREGIGNPC

**SEQ ID 15**

ATGGCATTTAAATTCCAGTTGAGGCTAAAAAATCAAGAAAGAGAAGGAATAGGGATCCTGCTAGGGGGCCACTGTAGAGCTCTAAACCC  
ATACCATTAACCTGGAAAACAGAAAACACAGTGTGGTAAATCAGTGGCCCTACAAAACAAAATGGGGTTTACATTATTAGCAATGAAC  
AGTTAGAAAAGGGTCAATTGAGCCTCTGGTCTCACCTTGGAAATTCTCTGTGTTGTAATTCAAGAAATCAGGCAATGGCTATGTTAATCTGA  
CTTAAGGGCTGTAACGCCGTAATTCAACCCATGGGCTCTCCACCCGGTGCCTCTCCGCATGATCCAAAAGATTGGCTTAAATTATA  
ATTGATCTAAAGGATTGCTTTTACCATCCCTGAGCAGGATTGGAAAAATTGCTTACTATACAGCCTAAATAATAAAAGAACAG  
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AAAGTTTCAGACTGTATATTATTCTATTGATGATATTGTCTGAGAACAGAAATTAATTGACTGTTATACATTCTGAA  
GCAGAGGTTGCAATGCTGAGTGGCAATAGCATGATAAGATCCAACCTCTACTCCTTTATTATTAGGATGAGATAGAAAATAGAAAAA  
TTAACCCACAAAAATAGAAAAGAACACATTAAACACTAAATGATTTCAAAAATTACTAGGGAGATATTAGGATTCGGCAACTCT  
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GACCAACCTATCAATTATCAGATTCTGCATATGTTAGTACAGGCTACAAGGGATGTTGAGACAGCTTAATTAAATATAGCATGGATGATCAGT  
TAAACCAAGCTATTCAATTATTACAACAAACTGTAAGAAAAGAAAATTCCCATTATTACACATATTGAGCAGCACACTAATTACAGGGC  
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GAGTAACTCCAGAGGTCTGTCCTAATGCAATTGGAAATGGATGTCACGCATGTACCTCATTGGAAAGATTATGTCACGTAACAGT

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 AAAGAAAAGCACCTCCGGAGAGGGAGACATCGCAATCGAGCACCGTGTACTCACAAGATGAACAAAATGGTACGTCAGAAGAACAGATGAAGTT  
 GCCATCCACCAAGAAGGCAGAGGCCAACACTGGGACAACTAAAGAGCTGAGCAGTTAGCTACAAAATCTAGAGAACACAAAGGTGACACAA  
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**SEQ ID 16**

ATGTTAACTGACTTAAGGGCTGTAACGCGTAATTCAACCCATGGGCCTCTCCACCCGGTTGCCCTCCGGCATGATCCAAAAGATTGGC  
 CTTAATTATAATTGATCTAAAGGATTGCTTTTACCATCCCTCGCAGACCGAGGATTGCAAAATTTGCTTTACTATACCAGCCATAAATAA  
 TAAAGAACCGCCACCCAGGTTCACTGGAAACTGTTACCTCAGGAAATGCTTAATAGTCACATTGTCAGACTTTGAGGTCGAGCTCTCAA  
 CCAGTAGAGAAAAGTTTCAGACTGTTATATTATTCTGATGATATTGCTGAGAAACGAAAGATAAAATTGACTGTTATA  
 CATTCTGCAAGCAGAGGTTGCCATGCTGGAATAGCATCTGATAAGATCCAACCTCTACTCCTTTCTATTATTAGGGATGAGATAGA  
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 CGGCCAACCTCTAGGCATTCTACTATGCCATGTCAAATTGTCCTATCTTAAGAGGAGACTCAGACTTAAATAGTAAAGAATGTAACCCAG  
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 CACTGCACTCTCCAAACAGGCATATTCAAAATACTGATCTGAGTTCAGCTACAGTAAAGACTTTACATTGAC  
 TTGGATCAAATAGCTACATTAATGGTCAGAACAGATTAGCAATAAATTATGTTGGAAATGACCCAGACAAAATAGTTGCTCCCTTAACCAAGG  
 AACAAAGTTAGACAAGCCTTATCAATTCTGGTCATGGAAGATTGTCCTGCTTAATTGTTGGAAATTATTGATAATCATTAACCAAAAACAAAGAT  
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 CAGATGAAGTGGCCATCCACCAAGAAGGCAGAGGCCAACCTGGGACAACTAAAGAGCTGAGCAGTTAGCTACAAAATATCTAGAGAACACAA  
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**SEQ ID 17**

ATGGCATTAAAGTCCCAACTGAGGCTGAAAAAAATCAAAAAAAGAAAAGGAATAGGGCATCTTTTAAAGCGGTACTGTAGAGCCTCCAAAACC  
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 GGGACTGACAATAGCATCTGATAAGGATTCAAACCTCTCCCTTCATTACTGGGAGTCAGGTAGAGGAAAAGGAAATTAAACCAACAAAATA  
 GAAATAAGAAAAGACACATTAAACATTAAAGTGGTGGAGATACTAATTGATTGGAGATAATTAAATTGGATTGGCAACT  
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 AAACCCAGTATTCAATTATTACACAAACTGTAAGAAAAGAAATTCCCAATTATTACTCATATTGAGCACACACTAATTACCCAGGGCCT  
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TAACAAACATTTGATGTCACATGGAAACAGGCCAAAGATATTGACAACTGGCACCAGTGTCAAGTCTTACACCTGTCACTCAAGAGCCAGGAGTTAACCTCCAGAGGTCTGTCTTAATGGCTTATGGCAATGGATGGCAGCAGTCTCTTCATTGGAAGATTATCATATGTCATGAAACAGTTGATACCTATTCACTATGGCAACTTGCCAAACAGGAGAAAGTACTTCCATGTTAAAACATTATTATCTGTTTGTGTAATGGAGTTCCAGAAAAATCATAACTGACAATGGACCAAGGATATTGAGTAAAGCTTCCAAAATTCTTAAGTCAGTGGAAATTTCACATACAACAGGAATTCTTATAATTCCAAGGACAGGCCATATTGAAAGAACTAATAGAACACTCAAACACTCAATTAGTTAAACAAAAGAAGGGGAGACAGTAAGGAGTGTACCACTCTCAGATGCAACTTAATCTAGCACTCTATACTTTAAATTTTAAACATTAGAAATCAGACTACTACTCTGCAAAACACATTACTGGTAAAGCACAGGCCACATGAAGGAAACTAATTGGTGAAAGATAATAAAAGACATGGAAATTAGGAAGGTGATAACGTGGGAGAGGGTTTGTGTTACCCAGGAGAAAATCAGCTTCCGTGTTGGATAACCCACTAGACATTGAGTTCTACATGAACCCATCGGAGATCAAGAAAGGGCTTCAAGAGATGGTAAACCCAGTCATGGATGGATAATC

SEQ ID 18

ATGGGGCCTCTCCAACCCGGGTTGCCCTCTCCGGCATGATCCAAAAGATTGGCTTTAATTATAATTGATCTAAAGGATTGCTTTTACCATCC  
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GGGAATGCTTAATGTCACATTGTCAGACTTTGAGGCTCTCAACAGTGGAGAGAAAAGTTTCAGACTGTTATTATTCTATT  
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CTGGTATCATCTGCACTCATAAAGCACAAGAATTCTCATGCTTTGACTCATGTAATTGCAAGCAGGATTAAAACAAATTGATGTCACATGGAAAC  
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GTCTGAGCATCACTGGGACATGGTTAGACGCCATCTACAGGGAAAGAGAAGATACTCAGACTTTAGACATTCCAAATTAAAGAACAAATTTCGAA  
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CCATTGGGAAGTACATCGATTATAATTCTCATATTAACTCTGTTGCTGCTGCTGTTGTTAGTCTGCAAGGTTGACCAACAGCTCCGAAGAGA  
CAGCGACCATCGAGAACGGGCCATGATGACGATGGGGTTTGTGCAAAGAAAAGGGGAAATGTGGGGAAAGCAAGAGAGATCAAATTGTTACT  
GTGTCGTTGAG

SEQ ID 19

MLTDLRAVNAVIQPMGQLPQGLPSPAMIPKDWPILLDLKDCCFTIPLAEQDCKEFAFTIPAINNKEPATRFQWKVLPQGMLNSPTICQTFVGRALQPVREKFSDCYIHIHICDDILCAETKDKLIDCYTFLQAEVANAGLAIASDKIQTSTPFHYLGMQIENRKIKPKQKIEIRKDTLKTLDNFQKLLGDINWIRPTLGIPTYAMSNLFSILRGDSLNSKRMLTPEATKEIKLVEEKIQSQAQINRIDPLAPLQLLIFATAHSPTGIIQONTDLVEWSFLPHSTVKTFTLY

LDQIATLIGQTRLRIIKLCGNDPKIVVPLTKEQVRQAFINSGAWKIGLANFVGIIIDNHYPKTKIFQFLKLTWILPKITRREPLENALTVFTDGSS  
NGKAAYTGPKERVIKTPYQSAQRAELVAVITVLQDFDQPINIISDSAYVQATRDVETALIKYSMDDQLNQLFNLLQQTVRKRNPFYIITHIRAHNT  
LPGPLTKANEQADLLVSSALIKAQELHALTHVNAAGLKNKFDTWQKQAKDIVQHCTQCQVLHLPQEAGVNPRGLCPNALWQMDVTHVPSFGRLSYV  
HVTVDYSHFIWATCQTGESTSHVKKHLLSCFAVMGVPEKIKTDNGPGYCSKAFQKFLSQWKISHTGIPYNSQGQAIVERTNRTLKTQLVKQKEGG  
DSKECTPQMQLNLALYTLNPLNIRNQTTSAEQHLTGKNSPHEGKLIWWKDSKNKTWEIGKVTWGRGFACVSPGENQLPVWIPTRHLKFYNEP  
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**SEQ ID 20**

MGPLQPGPLSPAMIPKDWPILLIDLKDCFFTIPLAEQDCEKFAFTIPAINNKEPATRFQWKVLPOGMILNSPTICQTFVGRALQPVREKFSDCYIIHY  
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FSILRGDSDLNSQRILTPPEATKEIKLVEEKIQSQAQINRIDPLAPLQLLIFATAHSPTGIIIQNTDLVEWSFLPHSTVKTFTLYLDQIATLIGQTRLR  
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KTPYQSAQRAELVAVITVLQDFDQPINIISDSAYVQATRDVETALIKYSMDDQLNQLFNLLQQTVRKRNPFYIITYIRAFTNLPGPLTKANEQADL  
LVSSALIKAQELHALTHVNAAGLKNKFDTWQKQAKDIVQHCTQCQVLHLPQEAGVNPRGLCPNALWQMDVTHVPSFGRLSYVHVTVDYSHFIWAT  
CQTGESTSHVKKHLLSCFAVMGVPEKIKTDNGPGYCSKAFQKFLSQWKISHTGIPYNSQGQAIVERTNRTLKTQLVKQKEGGDSKECTPQMQLNL  
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PVTWMDNPIEVYVNDSIWVPGPIDDRCPAKPEEEGMMINISIGYRYPPICLGRAPGCLMPAVQNWLVEVPTVSPISRFTYHMVSGMSLRPRVNYLQD  
FSYQRSLKFRPKGKPCPKESKNTEVLUWEECVANSAVILXNNENFGTIIDWAPRGQFYHNCQSGQTQSCPSAQVSPAVDSLTDKHHKKLQ  
SFYPWEWGEKGISTPRPKIVSPVSGPHEPELWRLTVASHHIRIWSGNQNTLETRDCKPFTVDLNSSLTVPLQSCVKPPYMLVVGNIIVIKPDSQTIC  
ENCRLLCIDSTPNWQHRIILLLVRAREGVWI PVSMDRPWEASPSPHILTEVULKVLRNRSKRFITLIAVINGLIAVTATAAVAGVALHSSVQSVNFVN  
DWQKNSTRLWNQSISIDQKLANQINDLRQTVIWMGDRIMSLERHQFLQCDWNTSDFCITPQIYNESEHHDMVRRLQGREDNLTDISKLKEQIFE  
ASKAHLNLVPGTEIAVADGLANLNPVTVWKTIGSTSIIINLILILVCLFCLLVCRCTQQLRRDSDHRERAMMTMAVLSKRKGNNVGKSKRDQIVT  
VSV

**SEQ ID 21**

NKSRKRNRNRESLLGAATVEPPKPIPLTWKTEKPVWVNQWPLPKQKLEALHLLANEQLEKHIEPSFSPWNSPVFVIQKKSGKWRMLTDLRNAVNIQ  
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CIDDILCAAETDKDLCDCYTFLQAEVANAGLAIASDKIQTSTPFHYLGMQIENRKIKPQKIEIRKDTLKLTLNDFQKLLGDINWIRPTLGIPTYAMSN  
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IIKLCGNDPKIVVPLTKEQVRQAFINSGAWKIGLANFVGIIIDNHYPKTKIFQFLKLTWILPKITRREPLENALTVFTDGSSNGKAAYTGPKERVI  
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TCQTGESTSHVKKHLLSCFAVMGVPEKIKTDNGPGYCSKAFQKFLSQWKISHTGIPYNSQGQAIVERTNRTLKTQLVKQKEGGDSKECTPQMQLNL  
ALYTLNFLNIRNQTTSAEQHLTGKNSPHEGKLIWWKDNKNKTWEIGKVTWGRGFACVSPGENQLPVWIPTRHLKFYNEPIGDAKKSTSATE  
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**SEQ ID 22**

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TATTCGCTAGGGAGAGCACCAGGTGTTAATGCCCTGAGTCACAAATTGGTGGTAGAAGTACCTACTGTCAGTCCCCTGAGTACCTT  
CACATGGTAACGGGAGTCACTCAGGCCACGGTAAATTATGAAAGACTTTCTTATCAAAGATCATTAAAATTAGACCTAAAGGAACCTT  
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AACTTTAGAAACAAGAGATCGTAAGCCATTAACTATTGACCTGAATTCCAGTCACAGTCCTTACAAAGTTGCTAAAGCCCCTTATATG  
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AACACCGTATTCTGCTGGTGAGACCAAGAGAGGGCGTGTGGATCCCTGTGTCATGGACCGTGGAGGCGCTCGCCATCCGTCCATTGGC  
TGAAGTAAAGGTGTTAAATGAGTCACCTTAACTTAACTGCACTTTAATTGCAAGTATGGGATTAAATGCACTGACAGTCACAGTCAGGCTGCT  
GTAGCAGGAGTTGCACTCTCTGTTGTCAGTCAGTAAACTTGTGAAATTGAGATTGGGAAAAATTCTACAAAGATTGCTGAATTCAACACTAGTA  
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GAAGATAATCTCACTTAGACATTCCAATTAAAAGAACAAATTTCGAAGCATCAAAGCCCATTTAAATTGGTAGCCAGGAACAGGGCAATTG  
CAGGAGTTGCTGATGGCCTCGCAAATTCTAACCCCTGTCACCTGGGTTAAGACCATGGAGACTACGATTAAATCTCATATTACCTTGTG  
CCTGTTGCTGTTAGTCGAGGTGACCCAAACAGCTCCGAAGAGACAGCGACCA

SEQ ID 23

ATGCAAAGAAAAGCACCTCCGGAGACGGAGACATCGAACCGTGACTCACAAGATGAACAAAATGGTGACGTCAAAGAACAGATGA  
AGTTGCCATCCACCAAGAAGGAGCAGAGCCGCAACTGGGCACAACTAAAAGAGCTGACGCAGTTAGCTACAAAATATCTAGAGAACACAAAGGTGAC  
ACAAACCCCAGAGAGTATGCTGCGACCTTGATGATTGTATCATGGTGTAGTCTCCCTATGCCCTGAGGAGCAGCTGAGCTAACTATACC  
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GCCCATAGATGATCGCTGCCCTGCCAACCTGAGGAAGAAGGGATGATGATAAAATATTCCTGGGTATCATTATCCTCCCTTGGCTAGGGAG  
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GAAAGTTAGACAAACATAAGCATAAAAATTGTCAGTCTTCTACCCCTGGATGGGAGAAAAGGAATCTCACCCCAAGACCAAAAATAGTAA  
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SEQ ID 24

TCATGGATGGATAATCCTATAGAAGTATGTTAATGATAGTGTATGGGTACCTGGCCCCACAGATGATCGCTGCCCTGCCAACACTGAGGAAG  
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AAGTACTATGATTAAATCTCATATTAACTCTGTCCTGTTGTTAGTCAGGTGACCCAAACAGCTCCGAAGAGACAGCAG  
CATCGAGAACGGGCCA

SEQ ID 25

ATGGGGCTCTCCAACCGGGTGCCTCCGGCATGATCCAAAAGATTGGCTTAAATTATAATTGATCTAAAGGATTGCTTTTACCATCC  
CTCTGCAGAGCAGATTGAAAAATTGCTTACTATACAGCCATAAAATAAAAGAACCCAGCCACAGGTTCAAGTGGAAAGTGTACTCTCA  
GGGAATGCTTAATAGTCAACTATTGTCAGACTTTGAGTCAGCTTCACCCAGTGGAGAAAAGTTCAAGCTGTATTATTATCATTAT  
ATTGATGATATTATGCTGCAGAACGAAAGATAATTAAATTGACTGTTACATTCTGCAAGCAGGGTGCCTAGCTGGACTGCATAG  
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 GTCTGAGCATCACTGGACATGGTAGACGCCATCTACAGGGAGAGATAATCTCATTAGACATTCCAAATTAAAAGAACAAATTGAA  
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 CCATTGGAAGTACATCGATTATAAACTCATATTAACTCTGCTGCTGCTGTTAGTCTGAGGTGACCCACAGCTCCGAAGAGA  
 CAGCGGACATGGAGACGGGATGAGCAGTGGGGTTTGTGAAAAGAAAAGGGGAAATGTGGGAAAAGCAAGAGAGATCAAATTGTTACT  
 GTGCTGTTAG

**SEQ ID 26**

MQRKAPPRRRRHNRNAPLTHKMNKMTSEEQMKLPSTKKAEPPTWAQLKKLTQLATKYLENTKVTQTPESMILLAALMIVSMVSLPMPAGAAAANYT  
 YWAYVPFPPLIRAVTWMNDNPEVYVNDSVWVPGPIIDRCPAKPEEGMMINISIGYHYPPICLGRAPGCLMPAVQNWLVEVPTVSPICRFTYHMVSG  
 MSLRPRVNYLQDFSYQRSLKFRPKGKPCPKEIPKESKNTEVILVWEVCVANSVILQNNFEGTIIDWAPRGQFYHNCSGQTQSCQSAQSPAVDSDLT  
 ESDLKHKHKKLQSFYWEKGKISTPRPKIVSPVSGPEHPELWRLTVASHHIRIWSGNQTLERDRKPFYTIIDLNSSLTVPLQSCVKPPYMLVVG  
 IVIKPDQSQTICNCRLLTCIDSTFNWQHRLVREGVWIPVSMDRPWEASPSVHILTEVLKGVLNRSKRFIFTIHAVIMGLIAVTATAAVAGVA  
 LHSSVQSVNFVNDWQKNSTRLWNSQSSIDQKLANQINDLRQTVIWMGDRLMSLHRFQLCDWNTSDFCITPQIYNESEHHWDMVRRHLQGREDNL  
 LDISKLKEQIFEAASKAHNLVPGTEAIAGVADGLANLPVTWVKTIGSTTIINLLILVLCLFCLLVCRCTQQLRSDHRRERAMMTMAVLSKRKGG  
 NVGSKRQIVTVSV

**SEQ ID 27**

MGPLQGLPSPAMIPKDWPLIIIDLKDCFTTIPILAECQDCEKFATIPIAINNKEPATRPFQWKVLPGMLNSPTICQTFVGRALQPVREKFSDCYIHY  
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 FSILRGDSDLNSQRILTPPEATKEIKLVEEKIQSQAINRIDLPLAPLQLLIFATAHSPTGIIQNTDLVEWSFLPHSTVKTFTLYLDQIATLIGQTRLR  
 ITKLCGNDPDKIVVPLTKEQVROAFINSGAWQIGLANFVGLINHYPKTKIFQFLKLTWILPKITRREPLENALTFTDGSSNGKAAYTGPKERI  
 KTPYQSAQRDELVAITVLDQDFQPINISDSAYVQATRDVETALIKYSMDQNLQFLNLLQQTVRKRNPFPYITYI RAHTNLPGLTKANEQADL  
 LVSSAIKAQEHLAHTHVNAGLKNKFDVTWKQAKDIVQHCTQCVLHLPTQEAGVNPRLGICPNAWQMDVTHVPSFCRLSYVHVTVDTYSHFIWAT  
 CQTCGSTSHVKKHLLSCFAVMVPEKIKTDNGPGYCSKAFQKFLSQWKISHTGTGIPYNSQGQAIVERTNRLTKLQVKQKEGDSKECTPQMQLN  
 ALYTLNFLNIYRNQTTSAEQLTGGKKNSPHEGKLIWWKDNKNTWEIKVITWGRGFACVSPGENQLPVWLPTRHLKFYNEPIGDAKKRASEMVT  
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 FSYQRSLKFRPKGKPCPKEIPKESKNTEVILVWEVCVANSVILQNNFEGTIIDWAPRGQFYHNCSGQTQSCPSAQSPAVDSDLTESLDKHKHKKLQ  
 SFYWPWEKGKISTPRPKIVSPVSGPEHPELWRLTVASHHIRIWSGNQTLERDRKPFYTVDLNSSLTVPLQSCVKPPYMLVVGNIIVKPDQSQTIC  
 ENCRLLTCIDSTFNWQHRLVREGVWIPVSMDRPWEASPSVHILTEVLKGVLNRSKRFIFTIHAVIMGLIAVTATAAVAGVALHSSVQSVNFV  
 DWQKNSTRLWNSQSSIDQKLANQINDLRQTVIWMGDRLMSLHRFQLCDWNTSDFCITPQIYNESEHHWDMVRRHLQGREDNLTDISKLKEQIF  
 ASKAHLNLVPGTEAIAGVADGLANLPVTWVKTIGSTTIINLLILVLCLFCLLVCRCTQQLRSDHRRERAMMTMAVLSKRKGGNVGSKRQIVT  
 VSV

**SEQ ID 28**

MNPSEMRKAPPRRRRHNRNAPLTHKMNKMTSEEQMKLPSTKKAEPPTWAQLKKLTQLATKYLENTKVTQTPESMILLAALMIVSMVSLPMPAGAA  
 AANYTYWAYVPFPPLIRAVTWMNDNPEVYVNDSVWVPGPIIDRCPAKPEEEGMMINISIGYHYPPICLGRAPGCLMPAVQNWLVEVPTVSPICRFTY

HMVSGMSLRPRVNYLQDFSYQRSLKFRPKGKPCPKEIPKESKNTEVLVWEECVANSAVILQNNEGTIIDWAPRGQFYHNCSGQTQSCPSAQVSPAV  
DSDLTESLDKHKHKKLQSFPWEWGEKGISTPRPKIVSPVSGPEHPELWRLTVASHHRIWSGNQTLERDRKPFYTIDLNSSLTVPLQSCVKPPYM  
LVVGNIVIKPDSQTITCENCRLLCIDSTFNWQHRIILVRAREGVWIPVSMDRPWEASPSVHILTEVLKGVLNRSKRFIFTLIAVIMGLIAVTATAA  
VAGVALHSSVQSVNFVNDWQKNSTRLWNQSISDQKLANQINDLQTVIWMGDRLMSLEHRFQLQCDWNTSDFCITPQIYNESEHHWDMVRRHLQGR  
EDNLTLIDISKLKEQIFEAASKAHLNLVPGEAIAGVADGLANLNPTWVKTIGSTTIINLILILVCLFCLLVCRTQQLRRSDHRERAMMTMAVL  
KRGGNVGKSKRDQIVTVSV

**SEQ ID 29**

AGTTCTACAATGAACCCATCAGAGATGCAAAGAAAAGCACCTCCGGAGACGGAGACATCGAACATCGAGCACCGTTGACTCACAAGATGAACAAAA  
TGGTGAACGTAGAAGAACAGATGAAGATTGCCATCCACCAAGAAGGCAGAGCCGCAACTTGGCACAACTAAAGAACGCTGACGCAGTTAGCTACAAA  
ATATCTAGAGAACACAAAGGTGACACAAACCCCAGAGAGTATGCTGCTGCAGCCTTGATGATTGTATCAATGGTGGTAAGTCTCCCTATGCCTGCA  
GGA

**SEQ ID 30**

TCTGCAGGTGTACCCAACAGCTCCGAAGAGACAGCGACCATCGAGAACGGGCCATGA

**SEQ ID 31**

MNPSEMQRKAPPRRRHRNRAPLTHKMNKMTSEEQMKLPSTKKAGPPTWAQLKLTQLATKYLENTKVTQTPESMLLAALMIVSMVSAGVPSNSSEE  
TATIENG

**SEQ ID 32**

MNPSEMQRKAPPRRRHRNRAPLTHKMNKMTSEEQMKLPSTKKAEPPPTWAQLKLTQLATKYLENTKSAGVPSNSSEEATIENG

**SEQ ID 33**

MNPSEMQRKGPPQRCLQVYPTAPKRQRPSRTGHDDGGFVEKKRGKCGEKQERSDCYCVCTERSRHRRLHFVLY

**SEQ ID 34**

MNSLEMQRKVWRWRHPNRLASLQVYPAAPKRQQPARMGHSDDGGFVKKRGYVRKREIRSLCLCRKGRHKKLHFVLY

**SEQ ID 35**

MNPSEMQRKAPPRRRHRNRAPLTHKMNKMTSEEQMKLPSTKKAEPPPTWAQLKLTQLATKYLENTKVLQVYPTAPKRQRPSRTGHDDGGFVEKKRGK  
CGEKQERSDCYCVCTERSRHRRLHFVLY

**SEQ ID 36**

MNPSEMQRKAPPRRRHRNRAPLTHKMNKMTSEEQMKLPSTKKAEPPPTWAQLKLTQLATKYLENTKVLQVYPTAPKRQRPSRTGHDDGGFVEKKRGK  
CGEKQERSDCYCVCTERSRHRRLHFVLY

**SEQ ID 37**

MNPSEMQRKAPPRRRHRNRAPLTHKMNKMTSEEQMKLPSTKKAEPPPTWAQLKLTQLATKYLENTKVTQTPESMLLAALMIVSMVYPTAPKRQR  
PSRTGHDDGGFVEKKRGKCGEKQERSDCYCVCTERSRHRRLHFVLY

**SEQ ID 38**

MNPSEMQRKGPPQRCLQVYPTAPKRQRPSRTGHDDGGFVEKKRGKCGEKQERSDCYCVCTERSRHRRLHFVLY

**SEQ ID 39**

MNPSEMQRKGPPQRCLQVYPTAPKRQRPSRTGHDDGGFVEKKRGKCGEKQERSDCYCVCTERSRHRRLHFVLY

**SEQ ID 40**

MEYKNRHLKFYNEPIGDAKKRASTEMSAGVPSNSSEEATIENG

**SEQ ID 41**

MNPSEMQRKGPPQRCLQVYPTAPKRQRPSRTGHDDGGFVEKKRGKCGEKQERSDCYCVCTERSRHRRLHFVLY

**SEQ ID 42**

MNPSEMQRKAPPRRRHRNRAPLTHKMNKMTSEEQMKLPSTKKAEPPPTWAQLKLTQLATKYLENTKSAGVPSNSSEEATIENG

**SEQ ID 43**

MNPSEMQRKAPPRRRHRNRAPLTHKMNKMTSEEQMKLPSTKKAEPPPTWAQLKLTQLATKYLENTKVTQTPESMLLAALMIVSMVSAGVPSNSSEE  
TATIENG

**SEQ ID 44**

MVTPVTWMDNPIEVYVNDSEWVPGPTDDRCPAKPEEEGMMINISIVYRYPPICLGRAPGCLMPAVQNCLQVYPTAPKRQRPSRTGHDDGGFVEKKR  
GKCGEKQERSDCYCVCTERSRHRRLHFVLY

**SEQ ID 45**

MVTPVTWMDNPIEVYVNDSEWVPGPTDDRCPAKPEEEGMMINISIGLQVYPTAPKRQRPSRTGHDDGGFVEKKRGKCGEKQERSDCYCVCTERSRH  
RRLHFVLY

**SEQ ID 46**

MNSLEMQRKVWRWRHPNRLASLQVYPAAPKRQQPARMGHSDDGGFVKKRGYVRKREIRSLCLCRKGRHKKLHFVLY

SEQ ID 47

MNSLEMQRKAPPRRRRHNRAPLTHKMKMVTSEEQMKLSSTKKAEPPPTWAQLKLTQLATKYLENTKVTQTPESMLAALMIVSMVVSLPMPAGAA  
AANYTYWAVYPFPPLIRAVTWMNDNPTEVYVNDSVWVPGPIDDRCPAKPEEEGMMINISIGYHYPPICLGRAPGCLMPAVQNWLVEPTVSPICRFTY  
HMSAGVPNSSEETATIENG

SEQ ID 48

MNPSEMQRKAPPRRRRHNRAPLTHKMKMVTSEEQMLPSTKKAEPPHTAQLKKLTQLATKYLENTKVTLQVYPTAPKRQRPSRTGHDDGGFVEKKRGKCGEKOERSDCYCVCVERSRRRLHFVMY

SEQ ID 49

MNPSEMQRKAPPRRRRHNRAPLTHKMKMVTSEEQMKLPSTKKAEPPTWAQLKKLTQLATKYLENTKVYPTAPKRQRPSRTGHDDGGFVEKKRGK  
CGEKOERSDCYCVCVERSRHRRLLHFVMY

SEQ ID 50

MNPSEMQRKAPPRRRRHNRAPLTHMKMKTSEEQMLKPSTKKAEPPWTAAQLKKLTQLATKYXLENTKVTQTPESMLAALMIVSMVVYPTAPKRQ  
RPSRTGHDDGGFVEKKRGKCGEKOERSDCYCVCVERSRHRRLHFVMY

**SEQ ID 51**

CCTGTCGGCTTCTCCCTCGGAAGCGTGGCGTTCTCATGCTCACGCTGTAGGTATCTCAGTCGGTGTAGGCGTTCGCTCCAAGCTGGC  
TGTGTCACGAACCCCCCGTTCAGCCCCACCGCTGCCCTTATCGGTAACATATCGCTTGAGTCACCCGTTAACGACAGCTATCGCCACTGG  
CAGCAGGCCACTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGGGTGCTACAGATTCTTGAAGTGGTGGCTAACTACGGCTACACTAGAAGGAC  
AGTATTTGGTATCTGCCCTCTGCTGAAGCCAGTTACCTTCGAAAAAGAGTGGTAGCTCTTGATCCGGAACCAAACACCACCGCTGGTAGCGTGGT  
TTTTTGTTGCAAGCAGATTACGCCAGAAAAAGGATCTCAAGAAGATCCTTGATCTTCTACTGAACGGTATCCCCACCGGAATTGC  
G

SEQ ID 52

**SEQ ID 53**

AGAGTCCACTATTAAGAACGTGGACTCCAACGTAAAGGGGAAAAACCGTCTATCGGGCGATGGCCGATCAGCTTATGGGTGTGAATACCG  
CACAGATCGTAAGGGAAAAATACCGCATCAGGGCTTCCGCTTCCGCTACTGACTCGCTCGCTCGGCTGGCTGGCTGGCGAGCGGTAT  
CAGCTCACTAAAGGGGTTAACGGTTATCCACAGAATCAGGGATAACCGAGGAAACATGTGAGCAAAGGCCAGCAAAGGCCAGGAACCG  
TAAAAAGGGCGGTGCTGGCTTTCCATAGGCTCCGCCCCCTGACGAGCATCACAAAATCGACGCTCAAGTCAGAGGTGGCAGAACCCGACA  
GGACTATAAGATAACCAGGGCTTCCCCCTGGAAAGCTCCCTGCGCTCTCTGTCGGACCCCTGCGCTTACCGATACTGTCGCCCTTCTCC  
CTTCGGGAAGCGTGGCCTTCTCATAGCTCACGCTGAGGTATCTCAGTTCGGTAGGTGCTCGCTCCAAGCTGGCTGTGTCACGAACCCCC  
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AGGATTAGCAGAGCGAGGTATGAGGGTGTACAGAGTTCTGAAGTGTGGCTAAGTACCGCTACACTAGAAGGACAGTATTGGTATCGG  
CTCTGCTGAAGCCAGTACCTCGGAAAAAGAGTGGTAGCTTGTACCGGAAACAAACCAACCCGGCTGGTAGCGGTGGTTTTTGTGCAAGCA  
GCAGATTACCGCAGAAAAAAGGATCTCAAGAAGATCTTGTACTGAAACGGTATCCCCACCGGAATTGCG

SEQ ID 54

CATGATGGATCTTCTGGCAGGAGCAAGGTGAGATGACAGGAGATCTGCCCCGGACTTCCCCAATAGCAGGCCAGTCCCTTCCCGCTCACTG  
ACAAACGTCGAGCACAGCTGCGAAGGAACGCCCTCGGCCAGCCACGATAGCCGCGTGCCTCGCAGTTCACTCAGGGCACCGGACAGGT  
CGGTCTTGACAAAAGAACCGGGCGCCCTGCGCTGACAGCGGAACACGGCGGATCAGAGCAGCCATTGTCGTTGCCCCAGTCAGATGCCGAA  
TAGCCTCTCCACCCCAAGCGCCGGAGAACCTCGTGCATCATTCTGTTCAATCATGCGAAACGATCCTCATCTGTCCTGATCAGATCTTGAT  
CCCCCTGCGCCATCAGATCTTGGCGCAAGAAAGCCATCCAGTTACTTGCAGGGCTTCCAACTTACAGAGGGCGCCAGCTGGCAATTCCG  
GTTCGCTTGTGTCCATAAAACCGCCAGTCTAGCTATGCCATGTAAGCCCAGTCAAGCTACCTGCTTCTTTCGCTTGCGTTTCCCTGT  
CCAGATAGCCAGTAGCTGACATTGATCCGGGGTCAAGCACCCTTCTGCGACTGGTTCTACGTGTTCCGCTTCCCTTACAGGCCCTGCGCCCT  
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GACGAGCATCACAAAATCGACGCTCAAGTCAGGGTGGCAGACAGGACTATAAAAGATACCAAGGCTTCCCTGGAGCTCCCTCGTGC  
GCTCTCTGTTCCGACCCCTGCCGCTTACCGGATACCTGTCGCCCTTCTCCCTCGGAAGCGTGGCTTCTCATAGCTACGCTGTAGCTATCT  
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TTTCTACTGAACGGTGATCCCCACCGGAATTGGC

SEQ ID 55

AAACGCCCGTCGTCGCCAGCCACGATAGCGCGCTGCCTCGCTCGAGTTCAATTAGGGCACGGGACAGTCGGCTTGCAGAAAAGAACCGGGCGC  
CCCTCGCGTACAGCGGAACACCGCGCATCAGAGCAGCGATTGTCGTTGTCGCCAGTCATAGCGGAATAGCCTCTCCACCCAAGCGGGCGGAG  
AACTCGCGTCAATCCATCTGTCATCATCGAAACGATCCTCATCCTGTCCTTGATCAGATCTTGATCCCTGCGCATCAGATCCTGGCGG  
CAAGAAAGCCATCCAGTTACTTTCAGGGCTTCCCACCTTACCAAGGGCGCCCCAGCTGGAAATCCGGTTCGCTGTCATCAAACCGCC  
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GTCTTGGCTGGCGAGCGGTATCAGCTCACTCAAAGGGTAAATACGGTTATCCACAGAAATCAGGGGATAACGAGGAAAGAACATGTGAGCAA  
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AAAGTCAGAGGTGGCGAACCCGACAGGACTATAAAGATACCAGGCCTTCCCCCTGGAAGCTCCCTGCGCTCTCCGTTCCGACCCGCGCTT  
ACCGGATACCTGTCGCTTCTCCCTCGGGAGCGTGGCGTTCTCATAGCTCACGCTGAGGTATCTCAGTCGGTGTAGGTCGTCGCTCCA  
AGCTGGGCTGTCGACGAACCCCCCGTTCAGCCGACCGCTGCGCTTACCGGTAACATCAGTCGGTGTAGGTCACCCGTAAGACACCGACTTATC  
GCCACTGGCAGCAGCACTGGTAACAGGATTAGCAGAGCGAGGTATGTAAGCGGTGTCAGAGTTCTGAAAGTGGTGGCTAACTACGGCTACACT  
AGAAGGACAGTATTGGTATCTGCGCTCTGCTGAAGCCAGTTACCTCGGAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCCACCGCTGGTA  
GGCGTGGTTTTTGTGCAAGCAGCAGATTACCGCAGAAAAAAAGGATCTAAGAAGATCCTTGATCTTCACTGAAACGGTGTACCCCA  
GGAATTGCG

**SEQ ID 56**

caagaccgcacacggccccggctactgcagcaaggcctccagaagttccctgagccagtggaaagatcagccacaccacccggcatccccataacacgc  
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AACGTCGAGCACAGCTGGCAAGGAACCCCGTCGTTGGCAGGCCAGATGCCGCGCTGCTCGTCACTGAGTCATTCAAGGGACCCGGAGGTG  
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GCCTCTCCACCCAAGCGGCCGAGAACCTCGTGCATCCATTTGTCATCATGCGAACAGCTCTCATCTGTCTCTGATCAGATCTGATCC  
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CGAGCATCACAAAATCAGCGCTCAAGTCAGAGGTGGCGAACCCGACAGGACTATAAGATACCGAGCGTTCCCTGGAAGCTCCCTGCGC  
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CCGGCAACAAACACCACCGCTGGTAGGGTGGTTTTTGTGCAAGCAGCAGATTACGCGCAGAAAAAGATCTCAAGAAGATCCTTGT  
TTCTACTGAGCGGTGATCCCCACCGGAATTGGC

**SEQ ID 57**

ATGAACCCATCAGAGATGAAAGAAAAGCACCCTCCGGAGACGGAGACATCGAATCGAGCACCGTTGACTCACAAGATGAAACAAATGGTGACGT  
CAGAAGAACAGATGAACTGGCATCCACCAAGAAGGCAGAGGCCAACTTGGGCACAACTAAAGAAGCTGACGCAGTTAGCTACAAAAATATCTAGA  
GAACACAAAGGTGACACAAACCCCCAGAGAGTATGCTGCTGCAGCCTGATGATTGATCAATGGTGTCTGCAGGTGACCCAAACAGCTCCGAAGAG  
ACAGCGACCATCGAGAACGGGCCATGA

SEQ ID 58

SEQ ID 59

ATGAACCCATCGGAGATCCAAGAAAAGCACCTCCGGAGACGGAGACATCGCAATCGACCGCTGACTCACAGATGAACAAATGGTGACGT  
CAGAAGAACAGATGAAGTTGCCATCCACCAAGAAGGCAGAGGCCAACCTGGGACAACATAAAAGAAGCTGACGCCAGTTAGCTACAAAATATCTAGA  
GAACCAAAGGTGACACAAACCCCGAGAGTATGCTGCTGCGAGCCTTGATGATTGATCATGGTGTACCCAAACGCTCCGAAGAGACAGCGA  
CCATCGAGAACGGGCCATGATGACGATGGCGTTTGTGCAAAAGAAAAGGGGGAAATGTGGGAAAAGCAAGAGAGATCAGATTGTTACTGTGCT  
GTGTAGAAAGAAGTAGACATAGGGAGCTCCATTGGTCTGACTAA

SEQ ID 60

ATGAGCCCCAGCGAGATGCAGCGAACGGCCCCCCCCGCCGCCGCCACCCGACCGCCTGACCCACAAGATGAACAAGATGGTACCC  
GCGAGGAGCAGATGAAGCTGCCAGCACCAAGAAGGCCAGCCCCACCTGGGCCAGCTGAAGAAGCTGACCCAGCTGGCACCAGTACCTGGA  
GAACACCAAGGTGACCCAGACCCCCGAGAGCATGCTGCTGGCCCCCTGATGATGAGCATGGTGGTGTACCCCAACGCCAGCGC

CCCCAGCCGACCGGCCACGACGACGCCGGCTTCGAGAAGAAGCGCGCAAGTGCAGGAGCGCAGCAGTCACTGCGTGT  
CCCCCTGGACCGCCACGCCACCGCCGGCTTCGACTTCGCTGTACGCTTAA

SEQ ID 61

ATGGGGCAACTAAAAGTAAAATTAAAGTAAATATGCCCTTATCTAGCTTATTAAAATTCTTTAAAAGGGGGAGTTAAAGTATCACAA  
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GGAATCAAACAGCAGGTAGGAAGGGATAATCATCCACTTACAGTATGGAATGTTGGCCATTATAAGCAGCTTGAACCATTCAAACAA  
GAAGAAGATAAGCTTCTGATGCCCTGGAGCTGTATAATAGATTGAAACAGGAAAGAACAGGAAAGGTT  
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CCTCAAAGCAGGTTAAAGAAAATAAGACCCAACCGCAGTAGCCTATCAATACTGGCTCCGGCTGAACTCAGTATGGCACCCCCAGAAAGTC  
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SEQ ID 62

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CCCCGCTGCAAGAACGCCAGGCAAGCACTGGGCCAGCCAGTGCCTGCAGCAAGAACGCCAGGCCCTGAGGCCAACGAGCACGCCAGG  
CCCAGGCCAGGCCAGAACGCCGCCCTCCCCATCCAGGCCCTGGTCCGCCAGGGCTTCCAGGCCAGCACGCCCTGAGGCCAGGTGTTCCAGGG  
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SEQ ID 63

ATGTGGGCAACATTGTGGAAACGAGCAAGGGCCAGCTCAGGCCACAAACTGGGCATTCCAATTAGGCCATTGTCTCAGGGT  
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ACGAGTCAAAAAATCATGACCAAGATGGGATATATACAGGAAAGGGACTAGGGAAAATGAAGATGGCATTAAATTCCAGTTGAGGCTAAAATAA  
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**SEQ ID 64**

ATGCCCCACCATCGGGCAAGCGCAGGGCCAGGGCCACCCACCAACTGGGCATCCCAACAGGCCATCTGCAGCAGCGCT  
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CGTGGACCTGTGACCATCCAGGCGTGAGCGTGCGCCGGAGCCCCCAGAAGACCCACCGCGTGATGGCCCTGCCAAGGGCACC  
GTGGGCTGATCCCTGGGCCAGCGCCAGACCTGAAGGGCGTGAGATCCACACCAGCGTGAGCAGCGACTACAAGGGCAGATCCAGCTGG  
TGATCAGCAGCAGCATCCCTGGAGGCCAGCCCCCGCAGCGCAGTGCCTAGCGCTGCTGCCATACATCAAGGGCGCAACAGCGAGATCAA  
GCGCATCGCGCCTGGCAGCAGGACCCACCGCAAGGCCACTGGGCAGCCAGGTGAGCAGAACGCCGCTGCAAGGCATCATC  
CAGGGCAAGCAGTGTGAGGCCCTGGGACACCGCGCCAGCGTGAGCATCATGCCCTGAACAGTGGCCAAGCAGAGGCC  
TGACCGGCTGTGGGATCGGCACCGCCAGCGAGGTGACAGAGCACCAGAGATCCGTGACTGCCCTGGGCCAGAACAGGAGGACCGTGCA  
GCCATGATCACAGCATCCCTGAACCTGTGGGCCAGCGACCTGTGAGCAGTGGGCCAGAGTACCATGCCGCCAGCTACAGCCCC  
ACCAAGCAGAAGATCATGACCAAGATGGCTACATCCCGCAAGGGCTGGCAAGAACGAGGACGGCATCAAGATCCCGTGAGGCCAAGATCA  
ACCAAGGAGCGCAGGGCATGGCAACCCCTGCGCTAA

**SEQ ID 65**

ATGATAATCAAGAAAGAGAAGGAATAGGGATCCTGCTAGGGCGCCACTGTAGAGCCTCTAAACCATACCTAACTGGAAAACAGAAA  
AACCAGTGTGGTAAATCAGTGGCCCTACAAAACAAAACAGGCTTACATTATTACAAATGAACAGTTAGAAAAGGTATATGAGCC  
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CAACCCATGGGCCCTCCACCCGGGTTGCCCTCCGGCATGATCCAAAAGATTGGCTTAATTATAATTGATCTAAAGGATTGCTTTTTA  
CCATCCCTGGCAGCAGGATTGCGAAAATTGCTTACTATACCAGCATAATAATAAAAGAACAGGCCACCCAGGTTAGTGGAAAGTGT  
ACCTCAGGAATGCTTAATAGTCAACTATTGTCAGACTTTGCTAGGTGAGCTTCACCCAGTTAGAGAAAAGTTTCAAGTGTATATTATT  
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CCAACCTGGGACAACATAAGAACGTGACGCAAGTAGCTACAAAATATCTAGAGAACACAAAGGTGACACAAACCCAGAGAGTATGCTGCTTGCAG  
CTTGTGATTGATCAATGGGTAAGTCTCCATGCCCTGAGGAGCAGCTGCAAGTAA

**SEQ ID 66**

ATGAAACAGAGCCGCAAGCGCCCAACCGCAGAGCCTGCTGGCGCCACCGTGGAGCCCCAAGCCATCCCCCTGACCTGGAAAGGCCAGA  
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CAGCTCAGCCCCCTGGAACAGCCCGTGTGATCCAGAAGAAGAGCGCAAGTGGCGCATGCTGACCGACCTGCCCGTGAAACCCGTGATC  
CAGCCCATGGCCCCCTGCAAGCCCGCTGCCAGCCCCGCAATGATCCCAAGGACTGGCCCTGATCATCATGACCTGAAGGACTGCTTCTCA  
CCATCCCCCTGGCCAGCAGGACTGCGAGAAATGCGCTTACCATCCCCGCAATCAACAAACAGGAGGCCACCCGCTCCAGTGGAAAGGTGCT  
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CACTGCACTGAGCACATCTGTGGCCCGAGACCAAGGACAAGCTGACTGCTACACCTTCTGCCAGGGCAGGTTGCCAACGCCGCTGG  
CCATGCCAGCAGAACAGATCCAGCAGCACCCCTTCAACTCTGGGATGCAAGGAGTCAAGGCCAGAAGATCAAGGCCAGAAGATGAGATCCG  
CAAGGACACCTGAAGACCTGAGCAGACTTCCAGAAGCTGCTGGGAGACATCAACTGGATCCGGCCACCCCTGGCATCCCCACCTACCCATGAGC  
AACCTGTTGAGCATCTGCGCGGAGCAGCGACCTGAACAGCAAGCGCATGCTGACCCCCAGGCCAGGAGATCAAGCTGGTGAGGAGAAGA  
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SEQ ID 67

MNPSEMORKAPRRRRHNRAPLTHKMNKMTSEEQMKLPSTKKAEPPTWAQLKKLTQLATKYLENTKVQTPESMILLAALMIVSMVSAGVPNSEE  
TATIENGPA

SEQ ID 68

MNPSEMQRKAPPRRRRHNRAPLTHKMNKMTSEEQMKLPSTKKAEPPTWAQLKLTQLATKYLENTKVTQTPESMILALMIVSMMVYPTAPKRQK  
PSRTGHDDGGFVEKKRGKCGEKQERSDCYCVCVERSRRHLFVLYA

**SEQ ID 69**

MGQTKSKIKSKYASLFSIKILLKRGGVKVSTKNLKLQFQIEQFCPNFPEQGTLQDKWKRICKELQAGRGNIIPLTVWNUWATIKAALEPFQI  
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PKQVKENKTQPPVAYQWPAPAELOQYRPPPESQYGPYGMPPAQGRAPYQPQPTRINPTAPPSRQGSKLHIIIDKSRKEGDEAWEAQFPVTLEPMPP  
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SEQ ID 70

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SEQ ID 71

SEQ ID MWATIVGKRAKGPGASPPTNWGIPNSAICSSGFSGTTPTVPSVGNKPVTIQQLSPATSGSAAVDLCTIQAVSLLPGEPPQKPTGVYGPLPKGT  
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SEQ ID 72

SEQ ID 72  
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QGKQFEGLVDTGADWSIALNQWPKNWPKQKAVTGLVIGTASEVYQSTEILHCLGPDNQESTVQPMITSIPLNLWGRDLLQQWGAETMPAPSYS  
TSOKIMTKMGYIPGKGLKKNEDGKIPVEAKINQEREGIGNPCA

SEQ ID 73

SEQ ID 75  
MNKSRKRRNRESLLGAATVEPPKPIPLTWKTEKPWVNVNQWPLPKQKLEALHLLANEQLEKGHIPESFSPWNSPVFVIQKKSGKWRMLTDLRAVNAI  
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**SEQ ID 74**

MNKSRRNRESLLGAATVEPPKPIPLTWKTEKPVWVNQWPLPKQKLEALHLLANEQLEKGHIEPSFSPWNSPVFIQKSGKWRMLTDLRAVNAVI  
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**SEQ ID 75**

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**SEQ ID 76**  
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 TAAATCAAGCTTACAGCAAAACCCATCTGCCCTGTGTCAAAATGTGAAAAGGAAAACATTGGGCAATCAATGTCATTCTAAATT  
 TGATAAGGATGGCAACCAATTGTCGGAAACAGGAAGAGGGCCAGCTCAGGCCCTGGCCCCCAACAAACTGGGCATTCCAGTCA  
 CAGGGTTCAAGGACAACAACCCCTACAGAAAATACCACCACTCAGGGAGTCAGCCAATTACAACATCCAACAGCTG  
 CAGCACCGCACTAA

**SEQ ID 77**

ATGGGCCAGCCGAGAGCAAGTACGCCAGCTACCTGAGCTCATCAAGATCCTGCGCCGGCGGTGCGGCCAGCACCAGAACCTGATCA  
 CCCGTTCCAGACCATCGCAGTTGCCCCCTGGTCCCCGAGCAGGGCACCTGGACCTGAAGGACTGGGAGAAGATCGCAAGGAGCTGAAGCA  
 GGCAACCGCGAGGGCAAGATCATCCCCCTGACCGTGTGAAACGACTGGGCCATCATCAAGGCACCCCTGGAGCCCTCCAGACCGGGGAGGACATC  
 GTGAGCGTGAGCGACGCCAGAAGAGCTGCGTACCGACTGCGAGGGAGGCCAGCAGGGCACCGAGAGCAGCCAGCAGGAGCTGCAAGT  
 ACCTGGCCAGAGCGTGATGGCCAGAGCACCCAGACGTGGACTACAGCCAGCTGCGAGGAGATCATCTACCCCGAGAGCACCAAGCTGGCGAGGG  
 CGGCCCCAGAGCGCTGGCCCCAGCGAGCCCAAGGCCCGAGCCCCAGCACCCCCCCCCCTGGTGAGATGCCGTGACCTGCAAGCCCCAGACC  
 CAGGTGCCAGGCCAGACCCCCCGAGAACCGAGTGGAGCGCGACCGCGTACATCCCCCATGCCACCCAGATCCAGTACCCCCAGTACCC  
 AGCCCGTGGAGAACAAGACCCAGCCCTGGTGGTACCAAGTACCGCTGCCACCCAGCTGCAAGTACCCGCCAGCAGCTGCAAGTACCCGCC  
 CCAGGCCGTGCCCCGTGCCAACAGCACCGCCCTACAGCAGCCACCGCCATGGCCAGCAACGCCAGCAGGCCACCCAGACGCCCTGTAC  
 CCCCAGCCCCCACCCTGCGCCTGAACCCACCGCCAGCGCAGCGCCAGGGCGGCCCTGCAAGCCGTGATCGAGCAGGCCAGCAAGCAGGGCG  
 ACCTGGAGGCTGGCGCTCTGGTACCTGCACTGGTGAGGCCAGGGAGACCCAGTGGGCCAGGGCGAGACCCAGTGGGCCAGGGCGAGACCCGCTGCA  
 GCCCTTACCATGAAGATGCTGAAGGACATCAAGGAGGGCGTAAGCAGTACCGCAGCAACGCCCTACATCCGACCCCTGCAAGGAGCTGCAAGTACCC  
 CACGGCAACCGCCTGACCCCTACGACTGGAGATCTGGCAAGAGCAGCCCTGCAAGCAGCAGGCCAGTACCTGCAAGTCAAGACCTGGTGGATCGACG  
 GCGTGCAGGAGCAGGGCGCAAGAACGAGGCCACCGCCAGGCCAGCGCCAGGGCGGCCCTGCAAGGCGACCCCAACTGGAGCACCAT  
 CAACCAAGCAGAGCGTGATCGAGAACGAGGCCATCGAGCAGGTGGCGCCATCTGCTGCGCCTGGGCAAGATCCAGGAGCCGGCACCGCTTC  
 CCCATCAACAGCATCCGCCAGGGCAGCAAGGAGGCCATACCCGACTTCTGGCCCGCTGCAAGGAGCCGGCCAGAAGAGCATACCGCAGCAACAG  
 CCCGCAAGGTGATCTGGAGCTGATGGCTACAGAGAACGCAACCCGAGTGCAGAGGCCATCAAGGCCCCTGCAAGGCAAGGTGCCCAGCGT  
 GGACGTGATCACCAGAGTACGTGAAGGCCTGCGACCCGAGTGCAGACCTGGGCCAGATCGGGCCAGTGGGCAACCAGTGGCACAGCAAGT  
 GCGGCCAGGTGGCACCTTGGCAAGAGTGTACAACACTGGGCCAGATCGGGCCAGTGGGCAACCAGTGGCACAGCAAGT  
 TCAACCAAGGCCATACCGCCAAGAACAGGCCAGGGCCCTGCCCCAAGTGGCGCAAGGCCAGGACTGGGCCACCAGTGGCACAGCAAGT  
 CGACAAGGACGGCCAGCCCCCTGAGCGGCAACCGCAAGCGCGGCCAGCCCCCAGCGAGACCCGGCCCTCCCCGTGCAAGTGTGCGCC  
 CAGGGCTTCCAGGGCCAGCAGCCCCCTGCAAGAACGATCCCCCCCCCTGCAAGGCCAGTGCAGCACAGAACAGTGGGCCAGGGCC  
 CGCCCCCCCAGGCTTAA

**SEQ ID 78**

MGQTESKYASYLSFIKILLRRGGVRASTENLITLFQTIQEFCPWFPPEQGTLDLKDEWIKGELKQANREGKIIPLTVWNDWAIIKATLEPFQGTGEDI  
 VSVDAPKSCVTDCEEAGTESQQGTESSHCKYVAESVMAQSTQNVDYSQQLQEIIPESKSLGEGGPESLGPSEPKPRSPSTPPVQMPVTLPQQT  
 QVRQAQTPRENVQERDRSIPAMPTQIYQPQYQPVENKTQPLVYQYRLPTEQYRPPSEVQYRPQAVCPVNSTAPYQQPTAMASNSPATQDAALY  
 PQPPTVRLNPTASRGQGGALHAIIDEARKQGDLEAWRFLVILQLVQAGEETQVGA PARAETRCEPFTMMLKDIKEGVKQYGSNSPYIRTLDSIA  
 HGNRLTPYDWEIILAKSSLSSQYLFQFTWIDGVQEVRKNQATKPTVNIDADQLLGTGPNWSTINQSVQMVNEAIEQVRAICLRAWGKIQDPTGAF  
 PINSIRQGSKEPYPDFVARLQDAAKSITDDNARKVIVELMAYENANPECQSAIKPLKGKVPAGVDVITEYVACADGIGGAMHKAMILMAQAMRGTL  
 GGQVRTFGKKCYNCGQIGHLKRSCPVLNKQNIINQAITAKNKKPSGLCPKCGKGKHWANQCHSKFDKDGQPLSGNRKRGQPQAPQQTGAFFPVQLFVP  
 QGFQQQPLQKIPPLQGVSQLQOSNSCPAPQQAAPQA

**SEQ ID 79**

MGQTESKYASYLSFIKILLRRGGVRASTENLITLFQTIQEFCPWFPPEQGTLDLKDEWIKGELKQANREGKIIPLTVWNDWAIIKATLEPFQGTGEDI  
 VSVDAPKSCVTDCEEAGTESQQGTESSHCKYVAESVMAQSTQNVDYSQQLQEIIPESKSLGEGGPESLGPSEPKPRSPSTPPVQMPVTLPQQT  
 QVRQAQTPRENVQERDRSIPAMPTQIYQPQYQPVENKTQPLVYQYRLPTEQYRPPSEVQYRPQAVCPVNSTAPYQQPTAMASNSPATQDAALY  
 PQPPTVRLNPTASRGQGGALHAIIDEARKQGDLEAWRFLVILQLVQAGEETQVGA PARAETRCEPFTMMLKDIKEGVKQYGSNSPYIRTLDSIA  
 HGNRLTPYDWEIILAKSSLSSQYLFQFTWIDGVQEVRKNQATKPTVNIDADQLLGTGPNWSTINQSVQMVNEAIEQVRAICLRAWGKIQDPTGAF  
 PINSIRQGSKEPYPDFVARLQDAAKSITDDNARKVIVELMAYENANPECQSAIKPLKGKVPAGVDVITEYVACADGIGGAMHKAMILMAQAMRGTL  
 GGQVRTFGKKCYNCGQIGHLKRSCPVLNKQNIINQAITAKNKKPSGLCPKCGKGKHWANQCHSKFDKDGQPLSGNRKRGQPQAPQQTGAFFPVQLFVP  
 QGFQQQPLQKIPPLQGVSQLQOSNSCPAPQQAAPQA

**SEQ ID 80**

GCGCGGAATTTCGACTCTAGGCCATTGCAACGGTGTATCTATATCATAATATGTACATTATATTGGCTCATGTCATATGACCGCCATGTTGA  
 CATTGATTATTGACTAGTTAAATAGTAATCAATTACGGGCTCATTAGTCATGCCCATATATGGACTTCCGCTTACATAACTTACGGTAAATG  
 GCGCGCTGGCTGACGCCAACGACCCCGCCATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTGACGTCA  
 ATGGGTGGAGTATTACGGTAAACTGCCACTTGGCAGTACATCAAGTGTATCATGCAAGTCCGCCCCCTATTGACGTCAATGACGGTAAATGG  
 CCCGCTGGCATTATGCCAGTACATGACCTTACGGACTTTCTACTTGGCAGTACATCACTGATTAGTCATGCCATTACCATGGTATGCGGT  
 TTTGGCAGTACACCAATGGCGTGGATAGCGGTTGACTCACGGGATTCCAAAGTCTCCACCCATTGACGTCAATGGGAGTTGTTTGGC  
 AAATCAACGGGACTTCCAAATGCGTAATAACCCGCCCTGACCAAATGGCGTAGGGCTGTACGGTGGAGGGCTATATAAGCAGAGCT  
 CGTTTACTGAACCGCTCAGATGCCCTGGAGACGCCATCCACGCTGTTTGACCTCCATAGAACGACCCGGGAGCCTCCGGGGGG  
 GGTGCATTGGAAACGGGATTCCCGTGCAGAGCTGACGTAAAGTACCGCTATAGACTCTATAGGCACACCCCTTGGCTTATGCTATGCTATACT  
 GTTTTGGCTGGGCTTACACCCCGCTTCTGCTATAGGTGATGGTATAGCTTACGGCTTACGGTGGGGTATGACCATATTGAC  
 TCCCTATTGGTACCGATACTTCTACTTACAGGATGGGCTCATTATTACAAATTCAACATACAAACGCGTCCCCCGTGGCCAG  
 AGACTGACACGGACTCTGTATTTACAGGATGGGCTCATTATTACAAATTCAACATACAAACGCGTCCCCCGTGGCCAG  
 TATTAACATAGCGTGGGATCTCACCGCAATCTGGGTACGTGGTCCGGACATGGGCTTCTCCGGTAGCGCGGGAGCTCCACATCCGAGCC  
 GGTCCCATGCCCTCCAGCGGCTCATGGCGCTCGGCAGCTCCCTGCTCTAACAGTGGAGGCCAGACTTGGCACAGCACAAATGCCACCCAC  
 ACCAG

SEQ ID 81

ATGAACCCAAAGCGAGATGCAAAGAAAAGCACCTCCGGAGACGGAGACATCGCAATCGAGCACCGTTGACTCACAAGATGAAACAAATGGTGACGT  
CAGAAGAACAGATGAGTTGCCATCCACCAAGAAGGCAGAGGCCAACCTGGGACAACATAAAGAAGCTGACGCAGTTAGCTACAAAAATATCTAGA  
GAACACAAAGGTGACACAAACCCCCAGAGAGTATGCTGCTGAGCCTGTATGATTGTATCAATGGTGGTAAGTCCTCTATGCCTGCAGGAGCAGCT  
GCAGCTAATATACTGGCTACTGGCTTCCGCCCTTAATTGGCAGTCACATGGATGGATAATCTACAGAAGTATATGTTAATGATA

GTGTATGGTACCTGGCCCATAGATGATCGCTGCCCTGCCAACCTGAGGAAGAAGGGATGATGATAAATATTCCATTGGGTATCATTATCCTCC  
TATTGCTAGGGAGGCACCAGGATGTTAATGCCCTGAGTCCAAATTGGTGGTAGAAGTACCTACTGTCAGTCCCCTGAGTATTCACTT  
CACATGGTAAGCGGGATGTCACTCAGGCCACGGGAAATTATCAAGACTTTCTTATCAAGATCATTAAATTAGACCTAAAGGGAAACCTT  
GCCCAAGGAAATTCCAAGAATCAAAAATACAGAAGTTAGTGGAGAATGTGTGGCAATAGTGGTGGTATATTACAAAACAATGAATT  
CGGAACATTAGATTGGCACCTCGAGGTCAATTCTACCACATTGTCAGGACAAACTCAGTCGTGTCAGTGCACAGTGGTCCAGTGT  
GATAGCGACTTAACAGAAAGTTAGACAAACATAAGCATAAAAATTGCACTTCTACCCCTGGGAATGGGAGAAAAGGAATCTCACCCAA  
GACCAAAATAGTAAGTCCTGTTCTGGCTGAACATCCAGAATTATGGAGGCTACTGTGGCTCACACCACATTAGAATTGGTCTGAAATCA  
AACTTAAAGAACAGAGATCGAAGCCATTATCACTATTGACCTGAATTCCAGTCAACAGTCCCTTACAAGTTGCGTAAAGCCCCCTTATATG  
CTAGTTGAGGAATAGTTATTAAACAGACTCCAGACTATAACCTGTGAAAATTGAGATTGCTTAATGCAATTGATTCAACTTTAATTGGC  
AACACCGTATTCTGCTGGTGGAGAGCAAGAGAGGGGTGTTGACCTGTCATGGACCGACCGTGGGAGGCGCTGCCATCCGTCATATTGAC  
TGAAGTATTAAAGGTGTTAAATAGTCAAAAGATTCACTTTAATTGCACTTGTGATTATGGGATTATTGCACTACAGCTACGGCTGCT  
GTAGCAGGAGTTGCACTCTGTCAGTCAAGTGGTAAATTCTACAAGATTGGAATTCAACATCTAGTA  
TTGATCAAAATTGCCAATCAAATTATGATCTAGACAAACTGTCATTGGATGGAGACAGACTCATGAGCTTAGAACATCCTTCAACTTACA  
ATGTCAGTGAATACGTCAAGATTGTTGATTACACCCAAATTATAATGAGTCAGGACATCACTGGGACATGGTTAGACGCCATCTACAGGAAAGA  
GAAGATAATCTCACTTGTGACATTCCAAATTAAAGAACAAATTTCGAAGCATAAAAGCCATTAAATTGGTCCAGGAACGGCAATTG  
CAGGAGTTGCTGATGGCCTCGCAATCTAACCCCTGTCACTTGGGTTAAGACCAATTGGAAGTACTACGATTATAATCTCATATTACCTTGTG  
CCTGTTTGTCTGTTAGCTGCAAGTGTACCCAACAGCTCCAGAGACAGCGACCATCGAGAACGGCCATGATGACGATGGGTTTGTG  
AAAAGAAAAGGGGAAATGGGAAAGCAAGAGAGATCAGATTGTTACTGTTGCTGTCCTAA

**SEQ ID 82**

ATGAACCCCAGCGAGATGCAGCGAAGGCCCGCCGCCGCCACCGCAACCGGCCACCGTGAACCCACAAGATGAACAAAGATGGTACCA  
GCGAGGAGCAGATGAAGCTGCCAGCCAAGAAGCCGAGGCCACCTGGCCAGCTGAAGAAGCTGACCCAGCTGGCCACCAAGTACCTGGA  
GAACACCAAGGTGACCCAGACCCCGAGAGCATGCTGCTGGCCCTGATGATCGTGAAGCATGGTGGTGAACCTGCCCAGTGCAGGCC  
GCCGCCAACTACACCTACTGGCCTACGTGCCCTCCCCCTGATCCGCCGTGACCTGGATGGACAACCCACCGAGGTGTACGTGAACGACA  
GCGTGTGGTGCCTGGCCATCGACGACCGCTGCCCGCAAGCCCGAGGAGGAGGGCATGATGATCAACATCAGCATGGCTACCAACTACCC  
CATCTGCCCTGGCCCGCCCGCTGCTGATGCCCGCCGTGAGAACTGGCTGTTGGAGGTGCCACCGTGAACCTGCCCAGTGCAGGCC  
CACATGGTGAAGCGGATGAGCTGCGCCCGCTGTAACCTGCACTTGCAGGACTTCAGCTACCGCGCAGCCTGAGTCCGCCAAGGGCAAGCC  
GCCCGAAGGAGATCCCAAGGAGAGCAAGAACACCCAGGGTGTGGGAGGAGTGCCTGGCAACAGCCCGTGATCTGCAAGAACACGAGTT  
CGGCACCATCATCGACTGGGCCCCCGCCGAGTCTACCAACTGCACTGGCCAGACCCAGAGCTGCCAGGCCAGGTGAGCCCCCGCTG  
GACAGCGACTGACCCAGAGCTGAGAACGACAAGAACACAGAGCTGCACTGGGAGGAGCTGCCAGGCCAGGGCATCAGCACCCCC  
GCCCGAAGTCGTGAGCCCCCGTGAGGGGCCAGACCCCGAGCTGTGGCCTGACCGTGGCCAGGCCACACATCCGCACTGGAGCGCAACCA  
GACCCCTGGAGACCCCGAGCCGAAGCCCTCTACCATCGACCTGAACAGCAGCTGCCAGGCCAGAGCTGCCAGGCCAGGTGAGCCCCCGCTG  
CTGGTGGTGGCAACATCGTGAAGCCGAACGACCATCACCTGCAAGGAACACTGCCCTGCTGACCTGCACTGACAGCACCTCAACTGGC  
AGCACCCGATCTGCTGGTGGCCCGAGGGCTGTGGATCCCCCTGAGCAGTGGACCGCCCTGGGAGGCCAGCCCGTGCACATCTGAC  
CGAGGTGCTGAAGGGCTGCTGAACCGCAGCAAGCGCTCATCTCACCTGATGCCGTGATCATGGGCTGATGCCGTGACCCGCC  
GTGGCCGGCTGCTGACAGCAGCTGAGGGTGAACCTGCTGAACCGCAGACCGTGTGGATGGGCAACAGCAGGCCCTGTGGAAACAGCAGC  
TCGACCAAGACTGGCAACCGATCAACGACCTGCCAGACCCAGGCTGACCTGGCTGACCTGCAAGGAGCTGCCAGGCCACCTGCAAGGGCC  
GTGCACTGGAAACACCCAGGACTCTGCACTACCCCGAGATCTACACAGAGCGAGCACCACTGGGACATGGTGGCCGCCACCTGCAAGGGCC  
GAGGACAACCTGACCTGGACATCGCAAGCTGAAGGAGCAGATCTGCAAGGAGCTGCAAGGCCACCTGAAACCTGGTGGCCGCCACCGAGGCC  
CCGGCGTGGCCGACGGCTGGCAACCTGAACCCCGTGAACCTGGGTGAAGACCATCGCAGCACCACATCAACCTGATCCTGACCTGGTGTG  
CCTGTTCTGCTGCTGGTGTGGCTGACCCAGCAGCTGCCCGCGAGCAGCACCGAGGCCATGATGACCCATGGCGTGCACATGGC  
AAGCGCAAGGGCGCAAGTGGCAAGAGCAAGCGCACCAGATGTCACCGTGAGCGTGGCTAA

**SEQ ID 83**

MNPSEMRKAPPRRRHRNRAPLTHKMNKMTSEEQMLPKSTKKAEPPTWAQLKKLTQKYLENTKVTQTPESMLLAALMIVSMVSLPMPAGAA  
AANYTYWAYVPFPPLIRAVTWMNPTEVYVNDSVWVPGPIDDRCPAKPEEEGMINISIGYHYPPICLGRAPGLMPAVQNLVEVPTVSPICRFTY  
HMVSGMSLRPRVNYLQDFSYQRLKFRPKGKPCPKIPEKSNTEVLWEECVANSAVILQNEFGTIIDWAPRGQFYHNSCGQTQSCPSAQVSPAV  
DSDLTESLDKHKHKKLQSFYPWEWGEKGISTPRPKIVSPVSGPEHPELWRITVASHHRIWNSGNQTLERDRKPFYTIDLNSSLTVPLQSCVVKPPM  
LVVGNIVIKPDSQTITCENCRLLT CIDSTFNWQHRIILVRAREGVWIPVSMDRPWEASPSVHILTEVLKGVLNRSKRFIFTI LIAVIMGLIAVTATAA  
VAGVALHSSVQSVNFVNDWQKNSTRLWNSQSSIDQKLANQINDLQTVIWMGDRILMSLEHRFQLQCDWNTSDFCITPQIYNESEHHDMVRRHLQGR  
EDNLTLIDISKLKEQI FEASKAHLNLVPGTEAIAGVADGLANLNPTWVKTIGSTTIINILILIVCLFCLLIVCRCTQQLRRSDHRRERAMMTMVLIS  
KRKGNGVGSKRDQIVTVSVA